Preparation of Hydrindenones from 2-Methylcyclopent-2-enone and the Carbanion of (*E*)-But-2-enyldiphenylphosphine Oxide: Efficient Enolate Trapping with β-Sulphonylvinyl Ketones

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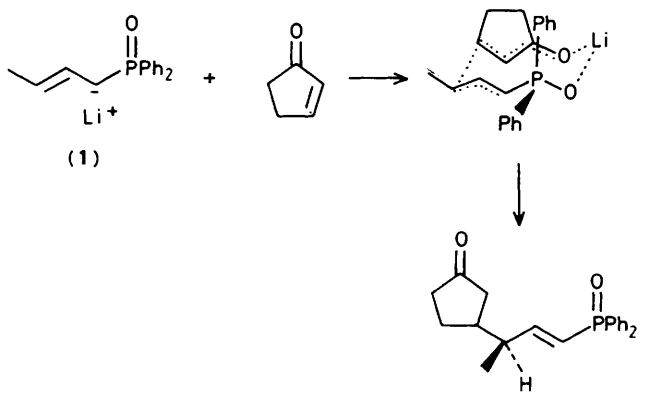
The β-sulphonylvinyl ketones (**5**), (**7**), (**9**), and (**10**), easily prepared from β-(phenylthio)propionyl chloride or from methyl vinyl ketone, react efficiently with the enolate produced by the conjugate addition of the carbanion of (*E*)-but-2-enyldiphenylphosphine oxide to 2-methylcyclopent-2-enone to provide in highly stereoselective fashion vinylogous β-diketones, two of which upon hydrogenation and aldol ring closure have been converted into hydrindenones in high yields.

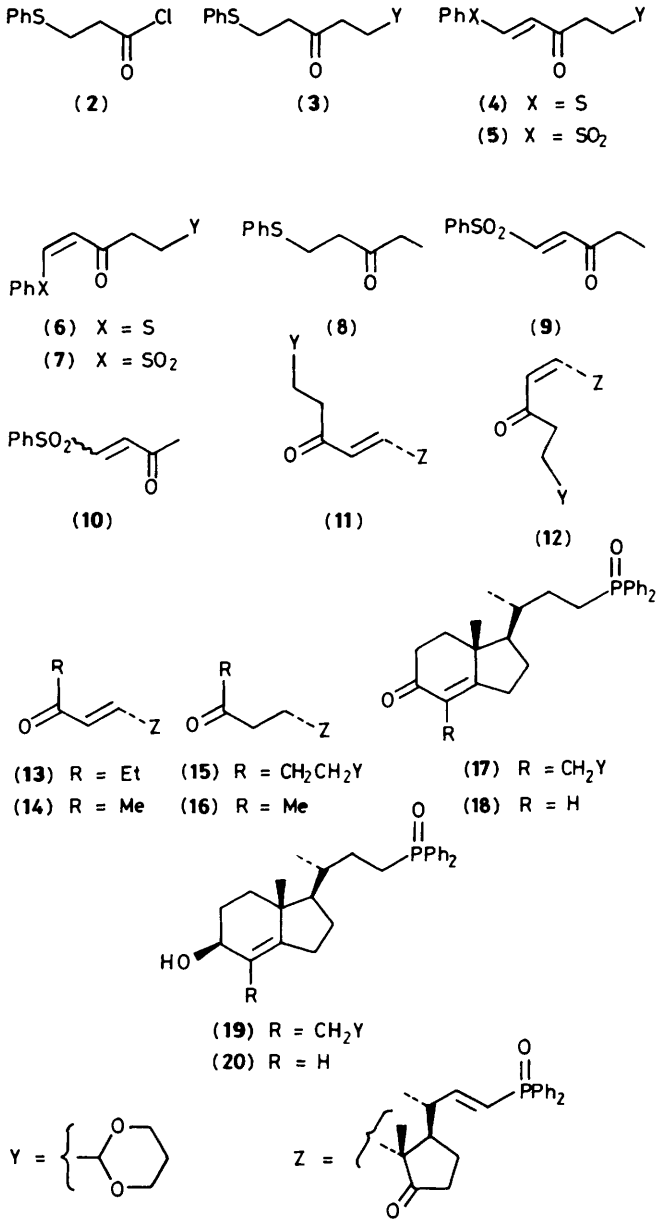
Allylic carbanions bearing alkyl groups at C-3 and charge-stabilizing groups such as sulphinyl and phosphinoyl at C-1 undergo aprotic conjugate addition to cyclopentenones to give single products whose regiochemistry and stereochemistry can be defined in terms of a '*trans*-fused chair–chair'-like transition state model such as that depicted for the reaction of the carbanion of (*E*)-but-2-enyldiphenylphosphine oxide (**1**) with cyclopentenone in Scheme 1.[1] By treatment of the enolate generated by the addition of the carbanion to 2-methylcyclopent-2-enone with the appropriate vinyl ketone



Scheme 1

equivalent, the stereospecific construction of hydrindenone precursors of steroid intermediates with the correct relative configuration at C-13, C-17, and C-20, and eventually at C-14, can in principle be carried out. The use of a conjugate addition–enolate trapping sequence for establishing the correct relative stereochemistry at these centres has been used previously.[2] However, the ease with which essentially pure, crystalline (*E*)-but-2-enyldiphenylphosphine oxide can be obtained[3]† coupled with the stereospecific outcome of the conjugate addition of its carbanion to cyclic enones makes it an ideal substrate. Nevertheless, the effective trapping of the enolate with vinyl ketone equivalents normally used under aprotic conditions is a problem associated with this approach. We herewith describe simple, stereospecific preparations of hydrindenones, which feature the use of β-sulphonylvinyl ketones as highly effective equivalents to the parent vinyl ketones.

Reaction of β-(phenylthio)propionyl chloride[4] (**2**) with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane[5] in tetrahydrofuran (THF) at −78 °C provided the ketone (**3**) (90%)‡ which was converted into the β-(phenylthio)vinyl ketone (**4**) by treatment with *N*-chlorosuccinimide and triethylamine.[6] Oxidation of (**3**) with *m*-chloroperbenzoic acid then gave the β-sulphonylvinyl ketone (**5**) (needles, m.p. 73—75 °C, from ethyl acetate–light petroleum [50% from (**3**)]. The recrystallised sample contained no detectable quantities of the (*Z*)-isomer (**7**). The latter was obtained from the neat liquid β-(phenylthio)vinyl ketone (**4**), which when kept at room temperature (*ca.* 20 °C) quantitatively isomerised to the crystalline (*Z*)-vinyl ketone (**6**) (needles, m.p. 85—86.5 °C, from light petroleum). This upon oxidation gave the isomer (**7**) (needles, m.p. 66—68 °C, from ethyl acetate–light petroleum). The β-sulphonylvinyl ketone (**9**) [needles, containing 5% of the (*Z*)-isomer, m.p. 87.5—89 °C, from ethyl acetate–light petroleum] was obtained by treatment of the acid chloride (**2**) with ethylmagnesium bromide in THF containing CuI at −78 °C, and desaturation–oxidation of the resultant ketone (**8**) as described above.



Conjugate addition of benzenethiol to methyl vinyl ketone and desaturation–oxidation gave the known[7] β-(benzenesulphonyl)vinyl methyl ketone (**10**) as a mixture of isomers (*E* : *Z* = 70 : 30).

The carbanion generated from the phosphine oxide (**1**) and butyl-lithium in THF at −50 °C was treated with 2-methylcyclopent-2-enone in the same solvent until disappearance of the red colour of the carbanion. The solution was then warmed to −20 °C, treated with the β-sulphonylvinyl ketone (**5**) (1.2 equiv.) and stirred for 5 min prior to quenching. The vinylogous β-diketone (**11**), which was obtained in a yield of 76% *from the phosphine oxide* (**1**), contained 3% of the (*Z*)-isomer (**12**) but no other diastereoisomer, according to its 400 MHz ^{1}H n.m.r. spectrum. The efficiency of this enolate trapping is remarkable, in view of the fact that protic quenching of the enolates generally gives the simple addition products in yields of 80—85%.[1] Surprisingly, the (*Z*)-sulphonylvinyl ketone (**7**) gave an equimolar mixture of the (*E*)- and (*Z*)-vinylogous β-diketones (**11**) and (**12**). The products

† The phosphine oxide is obtained as a 91 : 9 mixture of (*E*)- and (*Z*)-isomers from but-3-en-2-ol and chlorodiphenylphosphine according to the method of Savage and Trippett (ref. 3). Recrystallisation from ethyl acetate gives needles, m.p. 118—120 °C, containing <0.5% of the (*Z*)-isomer, according to 400 MHz ^{1}H n.m.r. spectroscopy.

‡ All new compounds have been fully characterised by high-field ^{1}H n.m.r. and other spectroscopic techniques and by microanalyses. Yields are quoted for compounds purified by chromatography and/or recrystallisation.

(**13**) and (**14**), obtained from the β-sulphonylvinyl ketones (**9**) and (**10**) in yields of 64 and 53%, contained small amounts [<3% for (**13**), 6% for (**14**)] of the (*Z*)-isomers. Use of methyl vinyl ketone itself or the α-trimethylsilyl derivative under the foregoing conditions either resulted in no enolate trapping or gave *ca.* 25% of the saturated ketone corresponding to (**14**).

The products (**11**) and (**14**) were hydrogenated (30—40 lb in^{-2}, Pd on C in ethyl acetate containing pyridine[8]) to the saturated adducts (**15**) and (**16**), aldol ring closure of which with KOH in refluxing methanol then gave the hydrindenones (**17**) [86% from (**11**)] and (**18**) [80% from (**14**)]. The hydrindenones were cleanly converted by di-isobutylaluminium hydride in CH_2Cl_2 at −50 °C into the hydrindenols (**19**) (75%) and (**20**) (75%).

As far as we are aware, the reaction of enolates with β-sulphonylvinyl ketones has not been described. Certainly, their reaction with β-halogenovinyl ketones is known,[9] but the outcome is far less satisfactory than it is in the case of the reactions described herein. As both hydrogenation and other methods of reduction[10] may be used to convert the vinylogous β-diketones formed in the enolate trapping into the saturated δ-diketones required for the aldol ring closure, the β-sulphonyl ketones must be seen as viable alternatives to other reagents traditionally used as equivalents to methyl vinyl ketone and its derivatives under aprotic conditions.

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