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METHYL 3-PHENYLSULFONYL ORTHOPROPIONATE : A NEW REAGENT FOR CYCLOPENTANNULATION

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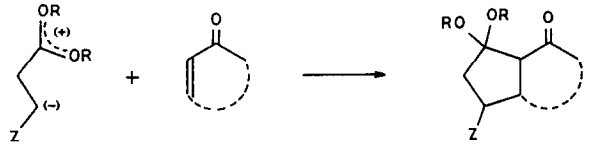
Summary : The title compound 1 is readily prepared by a Pinner reaction on the adduct of phenylsulfinic acid with acrylonitrile. The anion derived from 1 adds 1,4 to enones to give specific enolates which are trapped with trimethylsilyl chloride. The resulting trimethylsilyl enol ethers cyclise smoothly to give cyclopentannulated products in good yields.

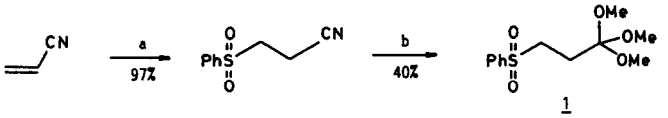
During the past decade, several methods for cyclopentannulation have been developed[1]. Our recent interest in homoenolate equivalents[2] suggested to us a synthetic route towards ketals of cyclopentanones by reaction of an enone with a synthetic equivalent of a stabilised 1,3 dipole[3](Scheme 1).



Z = electron-withdrawing group

Scheme 1

A suitable reagent is methyl 3-phenylsulfonyl orthopropionate 1 which combines a potential carbanion center at C-3, stabilised by a phenylsulfonyl substituent, with the masked cationic character of an orthoester function at C-1. Compound 1 was easily prepared on a multigram scale in two steps from inexpensive starting materials[4] (Scheme 2).



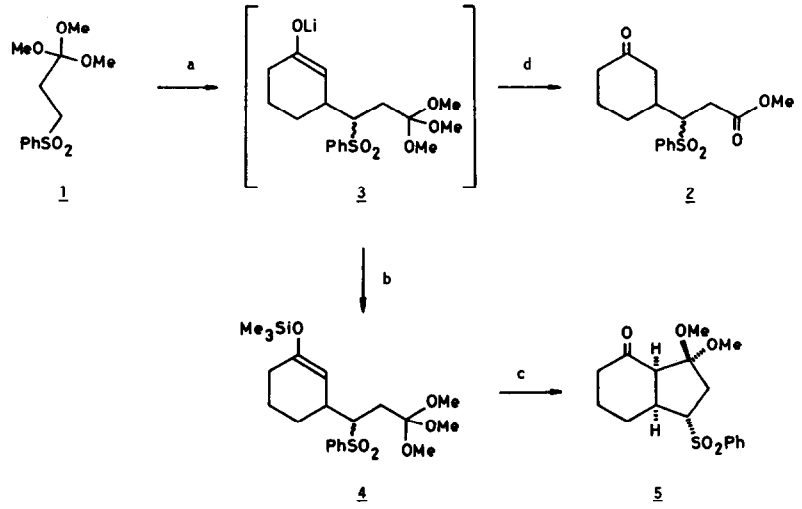
1

(a) : $PhSO_2Na$ (1.1 equiv.), AcOH (1.1 equiv), H_2O, 100°C, 15hrs[5].

(b) : MeOH (2.1 equiv.), AcCl (1.1 equiv.), CH_2Cl_2, 5°C, 45hrs; MeOH, 20°C, 72 hrs; KOH 2N, Et_2O, 20°C, 4 hrs.

Scheme 2

1 was readily deprotonated with n-BuLi in THF at - 78°C. Addition of cyclohexenone to the resulting anion yielded a complex mixture of 1,2 and 1,4 adducts and several unidentified products. However, when the reaction was carried out in THF containing 5 equiv. of HMPA[6], the 1,4 adduct was the major product as shown by the isolation of the ketoester 2 in 85% yield (Scheme 3). Thus, reagent 1 behaves as an efficient homoenolate equivalent that converts cyclohexenone into a 1,6 ketoester 2[7].



1 3 2

4 5

(a) : n-BuLi, THF, HMPA (5 equiv.), - 78°C, 30 min; Cyclohexenone, -78°C, 30 min.

(b) : Me_3SiCl (3 equiv.), NEt_3 (3 equiv.), - 78°C to 25°C then brine.

(c) : Me_3SiOTf (0.1 equiv.), CH_2Cl_2, - 78°C, 30 min.

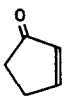
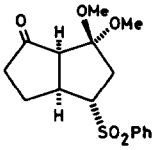
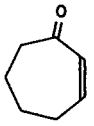
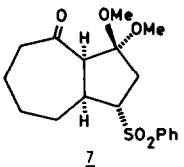
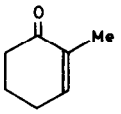
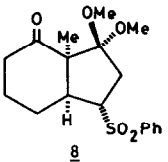
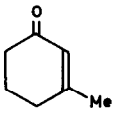
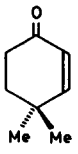
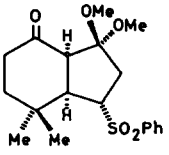
(d) : HCl 0.1N, 25°C, 15 min

Scheme 3

A Claisen-type cyclisation[8] of 2 was precluded by the presence of the base-sensitive phenylsulfonyl group. Therefore the specific lithium enolate 3 was trapped with trimethylsilyl chloride to give 4 which was washed with brine to remove HMPA[9]. Treatment of crude 4 with a catalytic amount of trimethylsilyl triflate[10] smoothly effected the cyclisation. Compound 5 was obtained in 68% overall yield as a single diastereoisomer.

The same conditions were applied to a series of enones (Table 1). The reaction is quite general. It is not sensitive to ring size and tolerates substitution at C-2 (entry C) and C-4 (entry E) of cyclohexenone but not at C-3 (entry D). 3-Methylcyclohexenone was deprotonated faster than it underwent 1,4 addition.

TABLE I : Cyclopentannulation of Enones

Entry	Enone	Product	Yield % [a]
A		 6	50
B		 7	65
C		 8	54
D		mixture of several products	
E		 9	60 [b]

a isolated and purified products ; from 1.

b the addition must be performed at 0°C. At -78°C, only the 1,2 adduct was formed.

Cyclopentannulated products 5 to 9 were obtained as single crystalline diastereoisomers with the configuration at the ring fusion being cis and the phenylsulfonyl substituent orientated in the exo position. This selectivity does not result from a fractionation during work-up or purification as shown by the examination of the 200 MHz PMR spectra of the intermediate silyl enol ethers and crude 5 to 9. Structural and stereochemical assignments were based on analyses of the 200 MHz PMR spectra and confirmed by X-ray diffraction analyses[11] of crystals of 7 and 8.

This simple route to configurationally pure cyclopentannulated products should find a number of useful applications. Two notable advantages of the method are (a) to form highly functionalised fused cyclopentanone derivatives, (b) to produce molecules in which the two ketone groups are differentiated.

References and Notes

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4. Compound 1 had previously been obtained earlier by a rather complicated route : W.E. Parham, W.D. Mc Kown, V. Nelson, S. Kajigaeshi and N. Ishikawa, J. Org. Chem., 38, 1361 (1973).
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7. See also : (a) P. Bakuzis, M.L.F. Bakuzis and T.F. Weingartner, Tetrahedron Lett., 27, 2371 (1978); (b) E. Nakamura and I. Kuwajima, J. Am. Chem. Soc., 106, 3368 (1984).
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9. No cyclisation occurred in the presence of HMPA.
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11. We thank Professors M. Van Meerssche and J.P. Declercq for the X-ray diffraction analyses which will be published separately.

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