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THE ATTEMPTED WITTIG REACTION OF SELENOPHOSPHORANES WITH KETONES: THE FORMATION OF 2-SELENOSUBSTITUTED KETONES

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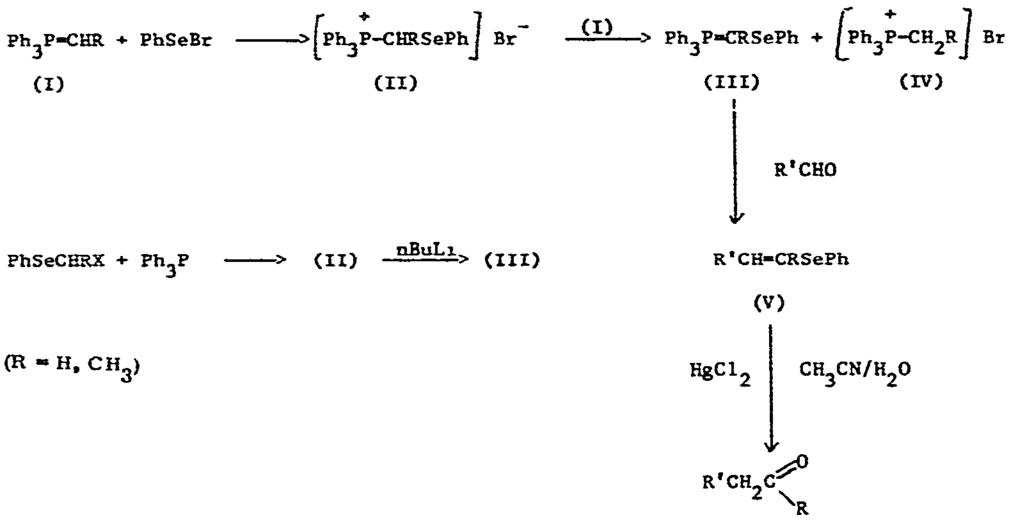
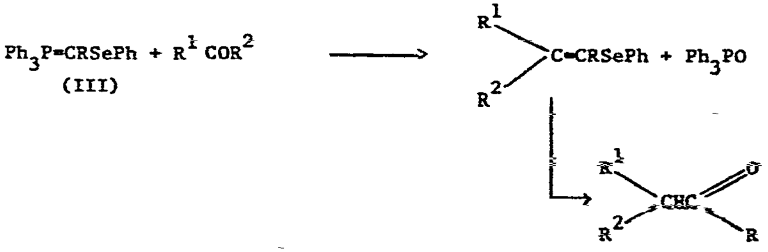
Summary Two α-phenylselenophosphoranes (III R=H or Me) were allowed to react with cyclohexanone giving instead of the expected olefinic Wittig product the corresponding 2-phenylselenocyclohexanone (VI). The reaction pathway has been demonstrated to involve nucleophilic substitution on selenium by the ketone enolate, the leaving group being the selenium free phosphorane (I) This reaction is shown to be general for seven more ketones, thus indicating its preparative potential.

Introduction In a preceding paper [1] we reported the preparation of triphenylselenophosphoranes (III) via transylidation between alkylidenephosphoranes (I) and PhSeBr, or by dehydrohalogenation of the corresponding selenophosphonium salts (II). The Wittig reaction of the selenophosphoranes with aliphatic and aromatic aldehydes produced the expected vinylic selenides, which then could be hydrolysed to the corresponding carbonyl compounds.



In view of these results, and of the literature reports describing the Wittig reaction of α-alkoxy and α-aryloxy phosphoranes [2-4] and their thio-analogs [5] with ketones, we had expected that the reaction of selenophosphoranes (III) with ketones would also give vinylic selenides*. Subsequent hydrolysis would then complete a general one-carbon atom homologation sequence.



However the reaction between the selenophosphoranes (II), and a series of ketones produced α-phenylseleno ketones instead. In this paper we report the results

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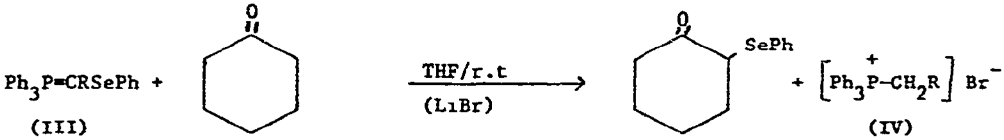
* The analogous α-silylphosphorane (Ph$_3$P=CHSiR$_3$) reacts with ketones giving

of our study of this reaction in which we demonstrate the reaction pathway and show its synthetic potential

Results and discussion

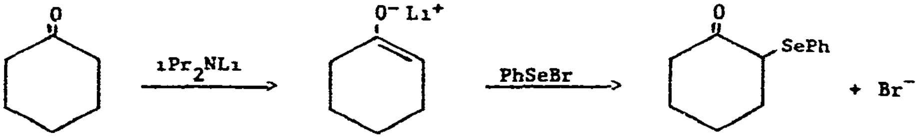
The reaction of the selenophosphoranes (III), prepared by either method, with cyclohexanone under the usual conditions gave an 80% isolated yield of 2-phenylselenocyclohexanone (VI) together with the selenium free phosphonium salt (IV) (in almost quantitative yield)



(III) (IV)

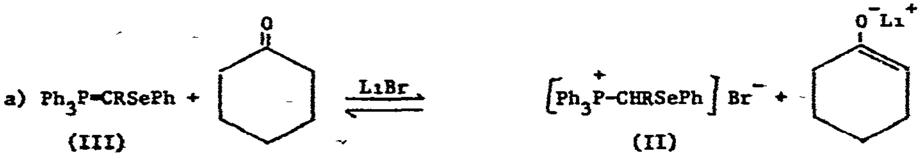
R=H,CH$_3$

The precipitation of (IV) can be most easily observed when (III) is obtained from (II) and n-BuLi, and is instantaneous at room temperature, showing that the reaction is very rapid. The ketonic product was compared with an authentic sample obtained by treating cyclohexanone enolate with PhSeBr [7,8].



(VII) (VI)

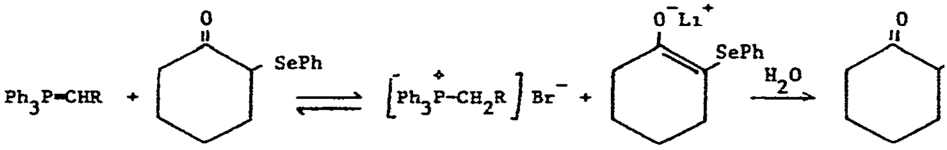
This unexpected result can be rationalized as follows:



(III) (II)

(VII)

c)



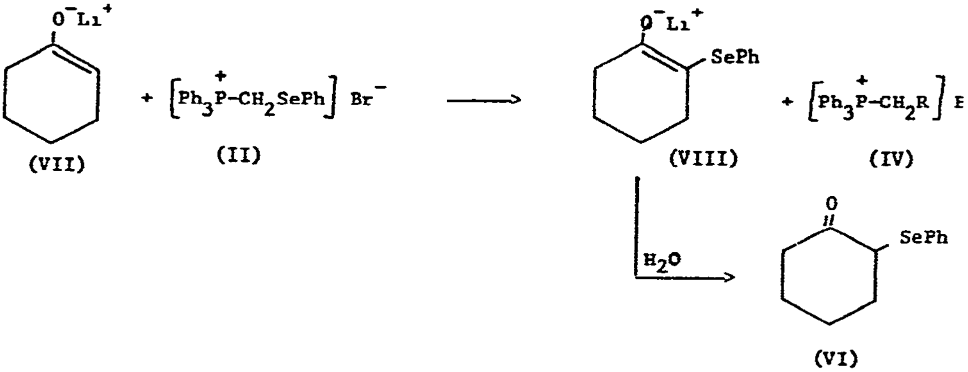
(I) (VI) (IV) (VIII) (VI)

Owing to the lower reactivity of ketones in comparison with aldehydes, the selenophosphorane (III), instead of adding to the carbonyl grou abstracts a proton from the ketone (step a), forming its enolate (VII) and the selenophosphonium salt (II). In view of the lack of exact pK_a data for phosphonium salts (IX), it is hard to predict the position of this equilibrium. The enolate (VII) then attacks the Se atom of (II), by nucleophilic substitutio giving the 2-phenylselenoketone (VI) and the Se-free phosphorane (I) (step b). This step is analogous to that involved in the preparation of authentic (VI) starting from (VII) and PhSeBr, differing only in the rather remarkable displacement of a non-stabilized phosphorane as the leaving group. Analogous behavior also has been observed in the reactions of 2-silylphosphonium salts with nucleophiles [10,11] under fairly mild conditions*. The preference of enolate attack at the Se atom of (II), instead of participating in an aldol condensation, is supported by the propensity of the selenium atom to suffer nucleophilic substitution reactions and the weakness of the C-Se bond (58 kcal/mol [13]). Proton exchange (step c) completes the sequence, this equilibrium being shifted to the right due to the stabilization of the 2-seleno-enolate (VI by the selenium orbitals, and the insolubity of the selenium free phosphonium salt (IV).

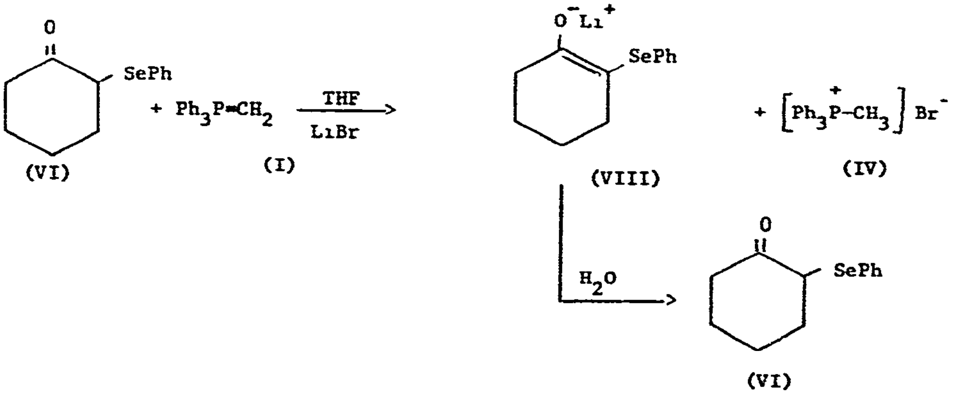
The proposed pathway was proved by investigating the individual steps in the reaction with cyclohexanone, as indicated in the following experiments:

1) Reaction of cyclohexanone enolate (VII), from cyclohexanone and iPr_2NLi, with the selenophosphonium salt (II; R=H).

[illegible]



2) Reaction of 2-phenylselenocyclohexanone (VI) with $Ph_3P{=}CH_2$ (I)

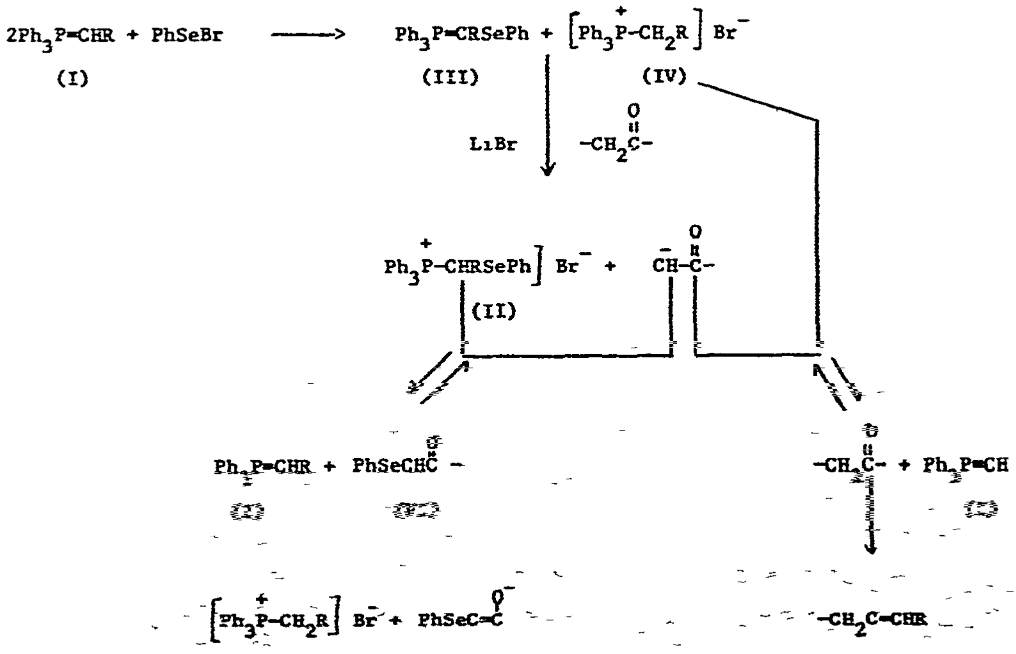


Both reactions gave results identical to those obtained in the main reaction, to be specific 2-phenylseleno cyclohexanone (VI) was isolated in 80% yield and the simple phosphonium salt (IV) in almost quantitative yield.

The generality of the reaction then was investigated using a series of cyclic and acyclic ketones. The table summarizes the yields and the analytical and spectral data of the products obtained.

It is interesting to note that all the ketones studied follow the same reaction pathway, whereas in the Wittig reaction, which works well with most ketones, it is known that cyclopentanone and acetophenone are prone of the less substituted selenium derivative (3:2 at 28° and 9:1 at 10°, as determined by NMR integration). This can be attributed to the formation of the kinetic enolate with the phosphorane base and this process obviously is temperatu dependent.

When the starting selenophosphoranes (III) were prepared <u>via</u> transylidation, it was observed (in some runs) that the presence of the insoluble phosphonium salt (IV) lowered the final yield of the 2-selenoketones, and filtration was therefore adopted as standard procedure This suggests that the two phosphonium salts (II) and (IV) can compete for the ketone enolate, (II) producing (VI) as already discussed, and (IV) regenerating the phosphorane (which then reacts with the ketone in a normal Wittig reaction In the case of acetophenone, we observed by NMR the formation of small quantities of the olefin (IX, $Ph(CH_3)C{=}CH_2$), and in separate experiments acetophenone enolate was allowed to react with triphenylmethylphosphonium bromide, producing the same olefin (IX). In the other cases the corresponding olefin was not observed, probably due to its volatility.



CONCLUSION

Although proton exchange also occurs in the Wittig reaction, this is to our knowledge the first example of a subsequent reaction between the enolate and the phosphonium salt The results obtained demonstrate three interesting facets which are emphasized by the extreme rapidity of the overall process the phenylseleno group on the ylide carbon dictates enolate formation of all the ketones studied, the enolates formed all prefer nucleophilic substitution on selenium to the aldol condensation, and methylenetriphenylphosphorane can be an effective leaving group under very mild conditions. However the results raise more questions than answers, especially the position of the first equilibrium and the basicity / nucleophilicity of the α-selenophosphorane. These, and other questions, will be the subject of future investigations

EXPERIMENTAL SECTION

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected NMR spectra were run on a Varian T60 spectrometer using tetramethylsilane as internal standart and CCl_4 as solvent. Infrared spectra were recorded on a Perkin-Elmer 457-A spectrometer. (Selenophenyl)methyltriphenylphosphonium bromide, selenophenol and phenylselenenyl bromide were prepared as described previously [1]. The products were purified by horizontal evaporative distillation on a Büchi Kugelrohrofen. Analytical samples were obtained by subsequent preparative thin layer chromatography.

1) Reaction of phenylselenophosphorane (III) with ketones - Typical procedure

a) *Via* transylidation

To a solution of methylenetriphenylphosphorane, prepared from methyltriphenylphosphonium bromide (1.7g, 0.005 mol) and n-BuLi (0.005 mol) in THF (5 ml) under nitrogen, was added dropwise at room temperature with magnetic stirring PhSeBr (0.59g, 0.0025 mol) in THF (3 ml). An orange solution containing reaction flask by means of a 45° curved tube charged with glass wool, and the ketone (0.0025 mol) added dropwise at room temperature. A crystalline precipitate formed instantaneously which after stirring for 1 hr was removed by filtration. The yellowish filtrate was washed with aqueous NH_4Cl and NaCl, dried with $MgSO_4$ and evaporated. The reaction mixture also can be diluted with petroleum - ether (30-50), the solvent decanted and the process repeated three times. The organic fraction was washed, dried and evaporated giving the product in the same yield but with increased facility of extraction and distillation. The residue was distilled *in vacuo* to give the 2-phenylselenoketone in the yield indicated in the Table.

The crystalline precipitates were identified separately as being the phosphonium salt (IV) by mixed mp and NMR spectra. In the run with acetophenone, the crude product contained traces of 2-phenylpropene (IX), as shown by NMR comparison with an authentic sample.

b) From the selenophosphonium salt (II)

To (selenophenyl)methylphenylphosphonium bromide (1.28g, 0.0025 mol) in THF (5 ml) was added dropwise n-BuLi (0.0025 mol) under nitrogen at room temperature with magnetic stirring. The ketone was added and the reaction performed as described in (a).

2) 2-phenylselenocyclohexanone (VI) from cyclohexanone

Lithium diisopropylamide was prepared from diisopropylamine (1.01g, 0.01 mol) in THF (10 ml) and the equivalent amount of n-BuLi, under nitrogen (0°. 15 min.). To this solution, cooled to -78°, was added cyclohexanone (0.98g, 0.01 mol), and after 15 min, PhSeBr (2.36g, 0.01 mol) in THF (5 ml). After 30 min. at -78°, the solution was diluted with petroleum ether (30-50)(25 ml), the solvent decanted, and the process was repeated three times. The organic layer was washed with saturated aqueous NH_4Cl, aqueous NaCl, dried ($MgSO_4$) and evaporated. The crude residue was distilled *in vacuo*, bp 132° (0,005 mm); yield 2.0g (80%). IR and NMR spectra of this product were identical with those of the product from the phosphorane (III) and cyclohexanone, and the data can be found in the Table with analytical data.

3) Reaction of cyclohexanone enolate (VII) with the selenophosphonium salt (II, R=H)

The cyclohexanone enolate (0.001 mole) was prepared as described in the preceding experiment. The solid salt (II; R=H) (0.512 g), 0.001 mol) was added at room temperature to this solution under nitrogen. After stirring for 1 hr, the crystalline precipitate which formed was removed by filtration (IV, R=H), (yield 0.35g, 100%, mp and NMR spectrum identical with those of an authentic sample) Normal work-up of the filtrate gave (VI); yield 0.20g (80%).

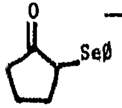
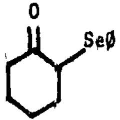
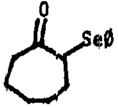
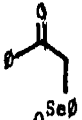
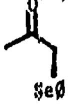
4) Reaction of phosphorane (I, R=H) with 2-phenylselenocyclohexanone (VI)

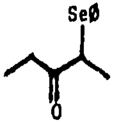
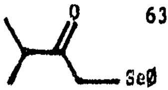
Methylenetriphenylphosphorane was prepared from methyltriphenylphosphonium bromide (0.714g, 0.002 mol) and n-BuLi (0.002 mol) in THF (10 ml), under nitrogen To this solution was added 2-phenylselenocyclohexanone (0 50g, 0 002 mol) at room temperature. The crystalline precipitate which formed was removed by filtration (IV; R=H), (yield 0 71g, 100%, m.p and NMR identical with those of an authentic sample). Normal work-up of the filtrate gave (VI), yield 0.40g (80%)

5) Reaction of acetophenone enolate with methyltriphosphonium bromide

To the enolate prepared from iPr_2NLi (1 equiv) and acetophenone (0.120g, 0.001 mole) in THF (10 ml), was added methyltriphenylphosphonium bromide (0.357g, 0.001 mole) at room temperature under nitrogen, and the mixture was allowed to react for 24h at room temperature. After normal work-up, 2-phenylpropene was indicated in the crude product by the following NMR peaks; $\delta(CCl_4)$2.10, 5.01 and 5.31. Repetition of the reaction (reflux 1.5h) permitted the isolation by preparative thin layer chromatography of pure 2-phenylpropene (30% yield). NMR $\delta(CCl_4)$2.10 (s,3H), 5.01 (m; 1H), 5.31(m, 1H), 7.10-7.52 (m, 5H).

TABLE

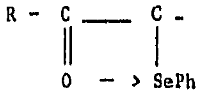
	yield(%)	bp	ANALYSES Found% (calcd.)% C	 Found% (calcd.)% H	NMR(δ)	ir(film)(cm^{-1})** ν c=O
	63^b	110°(0.01mm)	55.00 (55.26)	5.22 (5.01)	1.75 - 2.60 (m,6H) 3.53 - 3.80 (m,1H) 7.10 - 7 70 (m,5H)	1719
	80^a 80^b	100°(0.001mm)	57.04 (56.95)	5.77 (5.53)	1 40 - 3.20 (m,8H) 3 65 - 3.90 (m,1H) 7.00 - 7.60 (m,5H)	1700
	59^a 59^b	120° (0.005mm)	58.16 (58.45)	5.89 (5.99)	0 96 - 2.96 (m,10H) 3.69(dd,J=10,6Hz,1H) 7.10 - 7.63 (m,5H)	1682
	57^a	125°(0.001mm)	60.20 (59.81)	6 73 (6.40)	0 90 - 3.03 (m,12H) 3.60 (dd,J=7,7Hz,1H) 7.03 - 7.60 (m,5H)	1704
	73^b	140-5°(0.001mm)	61.17 (61.12)	4.45 (4 36)	4.05 (s,2H) 7.08 - 7.96 (m,10H)	1656
	40^a	60-5°(0.05mm)	50.76 (50.73)	4.95 (4 69)	2.20 (s,3H) 3 50 (s,2H) 7 20 - 7.60 (m,5H)	1700

	47^a 52^b	100°(0.005mm)	54.82 (54.80)	5.56 (5.80)	1.13 (t,J=7Hz,3H) * 1.51 (d,J=7Hz,3H) 2.49 (dq,J=7,17Hz,1H) 2.76 (dq,J=7,17Hz,1H) 3 76 (q,J=7Hz,1H) 7 13 - 7.63 (m,5H)	1690
	$63^{a,c}$	105°(0.005mm)	54.97 (54.80)	6.08 (5.80)	1.06(d,J=7Hz,6H) 2.86 (sp,J=7Hz,1H) 3.55 (s,2H) 7.06 - 7.58 (m,5H)	1685

method. a Transylidation
b Se phosphonium salts
c reaction performed at 10°

* The data for diethyl ketone show that the 2 methylene hydrogens are not chemically equivalent (ABX_3 spin system)

** The carbonyl stretching bands in the α-selenoketones are shifted to lower frequencies relative to the non substituted ketone. This may suggest a weak coordination of the carbonyl oxygen to the Se atom



$$R-\underset{O}{\underset{\|}{C}}-\underset{SePh}{\underset{|}{C}}-\quad O\rightarrow SePh$$

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