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WITTIG-HORNER REACTION OF A PHOSPHONATE OF REISSERT ANALOGUE
A NEW METHOD FOR INTRODUCTION OF ALKYL GROUPS INTO ISOQUINOLINE

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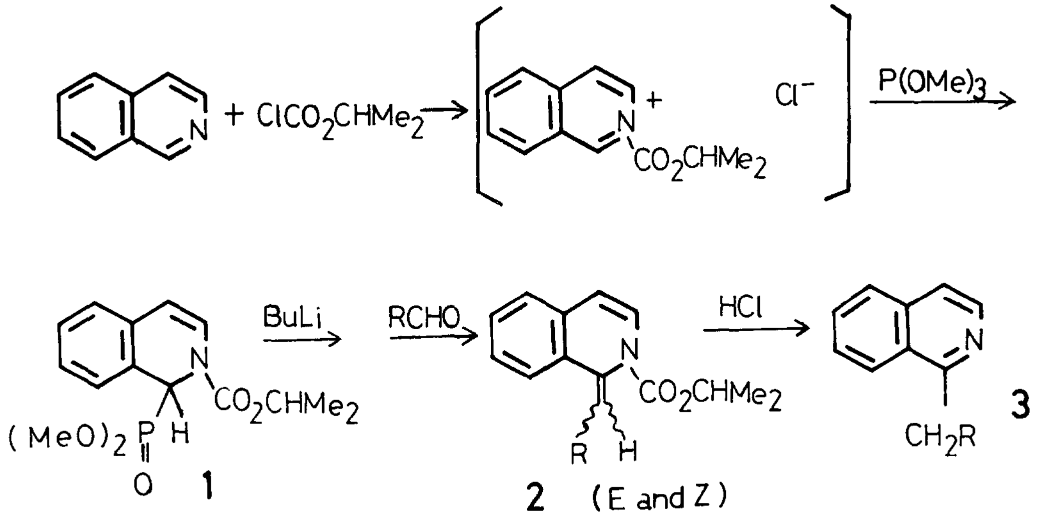
Abstract : Dimethyl 2-isopropoxycarbonyl-1, 2-dihydroisoquinoline-1-phosphonate (**1**) was prepared from isoquinoline, isopropyl chloroformate, and trimethyl phosphite. Wittig-Horner reaction of **1** with various aldehydes afforded the corresponding exo-methylene compounds, which were converted to 1-substituted isoquinolines with hydrogen chloride.

In pursuing to develop a generally applicable method to introduce substituents into heteroaromatics, we recently found a method to prepare a variety of heterocyclic phosphonates and to use them for carbonyl olefination to afford several kinds of heterocycles containing exo-methylene groups, or fulvalene-type derivatives, starting from the corresponding heteroaromatic cations.[2]

In order to extend this synthetic method to simple π-deficient heterocycles, an isoquinolinium salt was generated in situ to afford 1, 2-dihydroisoquinoline-1-phosphonate by Arbuzov reaction with trimethyl phosphite. The phosphonate thus obtained is an analogue of Reissert compounds where the phosphonyl group is substituted for the cyano group.[3] A typical example is described below.

Dimethyl 2-isopropoxycarbonyl-1, 2-dihydroisoquinoline-1-phosphonate (**1**, mp 53.0-54.0 °C, 76%) was prepared by the reaction of the isoquinolinium salt, which was generated in acetonitrile (30 ml) from isoquinoline (47 mmol) and isopropyl chloroformate (47 mmol), with trimethyl phosphite (47 mmol) in the presence of sodium iodide (53 mmol) according to the procedure described before.[4]



Several aldehydes reacted with the carbanion of **1** to afford the corresponding exo-methylene compounds (**2**) by Wittig-Horner reaction. In a typical run, butyllithium (1.1 equivalent, hexane solution) was added to **1** (4.5 mmol) in tetrahydrofuran (THF, 10 ml) below -70 °C, then p-tolualdehyde (4.5 mmol) was added with stirring and the temperature of the solution was allowed to rise to room temperature. After usual work-up, the residue was subjected to dry column chromatography (DCC) (Merck, neutral alumina, ether-hexane = 1 : 1), the exo-methylene product (**2b** : 63% as a mixture of E and Z isomers) was eluted first followed by a small amount (11%) of 1-(p-methylbenzyl)isoquinoline (**3**).[5)]

E isomer (**2**) was the major product of Wittig-Horner reaction and accompanied with a small amount of Z isomer. E isomer turned to Z isomer by heating or during chromatographic purification and both isomers were separated and characterized in some cases as shown in the Table. The assignment is based on the fact that the doublet of the methyl of the isopropyl group appears at a higher field with slight broadening for Z isomer when R is an aryl group, compared to that of E isomer according to the shielding effect of a phenyl ring. This assingment was confirmed by the fact that the corresponding doublet of **2** prepared from **1** and 4, 4'-dichlorobenzophenone appeared at the higher field with some broadening.

The exo-methylene compound (**2b**) was converted to the hydrochloride of 1-(p-methylbenzyl) isoquinoline (**3b**) almost quantitatively by introduction of hydrogen chloride to the ethereal solution at room temperature for 10 min and also by warming (30-40 °C) ethanol solution containing excess amount of hydrochloric acid for 30 min. Thus this method offers a new facile procedure to introduce substituents at 1-position of isoquinoline using aldehyde.5)

When quinoline was used instead of isoquinoline, the phosphonate and the exo-methylene compound corresponding to **1** and **2b** were obtained in somewhat lower yields, i.e., 56 (pale yellow oil) and 40% (mp 45-105 °C, a mixture of E and Z isomers) yields, respectively.

Table Yields and Characterization of the Exo-methylene Compounds (**2**)

2 R	Total Yield (%)1)		mp (°C)	Ratio of E / Z	^{1}H NMR4) -CH$\underline{Me}_2$	$\begin{matrix}R\\ \underline{H}\end{matrix}\!>\!C=$
a) p-$MeOC_6H_4$	81	E	—	4	1.36	6.67
		Z	127.0-127.5 (B-H)2)		0.94	6.43
b) p-MeC_6H_4	63	E	74.8- 76.3 (D-H)	3	1.35	6.90
		Z	172.4-173.4 (A)		0.91	6.47
c) C_6H_5	87	E	—	3	1.37	6.91
		Z	130.0-131.0 (B-H)		0.90	6.49
d) p-ClC_6H_4	66	E	84.0- 88.0 (E-H)	1	1.38	6.87
		Z	132.0-132.5 (B-H)		0.94	6.43
e) n-Pr	46	E	oil as a mixture	53)	1.30	5.80
		Z			1.30	5.69
f) i-Pr	61	E	oil as a mixture	2.53)	1.12	5.57
		Z			1.06	5.35
g) t-Bu	53	E	oil as a mixture	43)	1.16	5.78
		Z			1.19	5.51

1) After DCC separation (see the text) 2) Sovent for recrystallization : B, benzene; H, hexane ; D, dichloromethane ; A, ethyl acetate ; E, ether 3) The ratio after DCC separation, hence the original ratio should be higher than that described here 4) Measured in $CDCl_3$ (δ). Chemical shifts are shown for the methyl group of the isopropoxycarbonyl group and the vinyl proton of the exo-methylene group.

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References and Notes

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2) (a) K. Ishikawa, K. Akiba, and N. Inamoto, *Tetrahedron Lett.*, **1976**, 3695.
(b) K. Akiba, K. Ishikawa, and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **51**, 2674, 2684 (1978) and references cited therein.

3) Compound (**1**) is a variation of Reissert compounds and reactions and some utility of the latter have been examined : see F. D. Popp in " Advances in Heterocyclic Chemistry " ed. by A. R. Katritzky, and J. A. Boulton, Academic Press, New York, 1968, Vol. **9**, p 1. However, potential utility of the present phosphonate (**1**) has been overlooked. When benzoyl and p-toluenesulfonyl groups are used instead of isopropoxycarbonyl group, **1** undergoes the same type of reaction as the corresponding Reissert compounds, therefore they are of no value for the present purpose. When ethoxycarbonyl group was used, the yield of **2b** was lower (ca. 50%) and some by-products were also obtained.

4) Preparation of analogous heterocyclic phosphonates has been described by us : K. Akiba, Y. Negishi, and N. Inamoto, *Synthesis*, **1979**, 55.

5) In every case, about 10% of **1** has been recovered in spite of careful check of reaction conditions, however **1** is easily separated from **2** and **3** by simple chromatography and the mixture of **2** and **3** is treated with HCl to give **3** for synthetic purpose. The hydrolysis here is much easier than that of Reissert compound : see B. C. Uff, J. R. Kershaw, and J. N. Neumeyer, *Organic Synth.*, **56**, 19 (1977).

6) All **1** and **2** gave correct elemental analyses. When pure E- or Z-isomer was obtained, combustion analysis was performed for each isomer. Otherwise, it was done for the mixture of both isomers.

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