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A STEREOSELECTIVE SYNTHESIS OF (Z)-1-IODO-1-ALKENES

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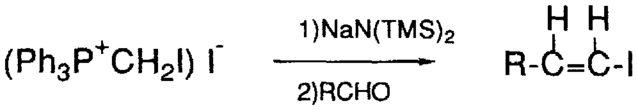
Abstract: *(Z)-1-iodo-1-alkenes can be synthesized stereoselectively via the Wittig reaction of iodomethylenetriphenylphosphorane with aldehydes.*

Vinyl halides of defined stereochemistry are useful building blocks for the synthesis of substituted olefins, some of which have important biological activity.[1] Multistep syntheses via alkynyl compounds[2] can often serve the purpose, but our synthetic work on histrionicotoxin emphasized the desirability of simpler routes, especially to Z-vinyl halides. One carbon homologation of aldehydes, using chloro- or bromomethyl Wittig reagents shows little stereoselectivity,[2] but the importance of vinyl iodides in synthesis led us to study the reaction of iodomethyltriphenylphosphorane with aldehydes. We have reexamined the possibility of making this phosphorane from the related phosphonium iodide,[3] using a variety of solvents (dioxane, benzene, DME, THF) and bases (t-BuOK, LDA, lithium or potassium hexamethyldisilazane and lithium piperidide) and have now found that the required phosphorane can be made readily by the use of sodium hexamethyldisilazane as base, in tetrahydrofuran solution. It is especially gratifying that the reaction of the phosphorane with a variety of aldehydes leads, stereoselectively, to (Z)-1-iodo-1-alkenes.



$$(Ph_3P^+CH_2I)\,I^- \xrightarrow[2)RCHO]{1)NaN(TMS)_2} R\text{-}\overset{H}{C}{=}\overset{H}{C}\text{-}I$$

Results for a number of aldehyde and ketone substrates are shown in the table. Treatment of iodomethyltriphenylphosphonium salts in dry THF with an equimolar amount of sodium hexamethyldisilazane, under an inert gas atmosphere at room temperature, yielded iodomethylenetriphenylphosphorane which reacted with aldehydes to afford the desired 1-iodoolefins. The stereoselectivity of the iodoolefins depends on the reaction temperature. For example, in the formation of (2-iodoethenyl)cyclohexane, the ratio of Z/E-isomer changed from 6:1 at -23 °C to 11:1 at -78 °C. It was increased to 15.5:1 when the aldehyde was added to the ylide solution at -78 °C, in the presence of HMPA.

Conversion of Carbonyl Compounds to Vinyl Iodides

Carbonyl Compound	Solvent	ylide generation		reaction	Yield[b]	*Z/E*[c]
		temperature	time	temperature[a]		
Methyl 6-oxohexanoate	THF	-23°C	8 min.	-23°C	74%	20:1
Citronellal	THF	-23°C	8 min.	-23°C	63%	12:1
Cyclohexanone	THF	-23°C	8 min.	-23°C	61%	
benzaldehyde	THF	-23°C	8 min.	-23°C	60%	4.6:1
	THF	20°C	1 min.	-78°C	63%	13:1
	THF/HMPA	20°C	1 min.	-78°C	96%	62:1
Nonyl aldehyde	THF	-23°C	8 min.	-23°C	76%	7.8:1
	THF	20°C	1 min.	-78°C	81%	8.3:1
	THF/HMPA	20°C	1 min.	-78°C	83%	9.4:1
Cyclohexanecarboxaldehyde	THF	-23°C	8 min.	-23°C	74%	6:1
	THF	20°C	1 min.	-78°C	72%	11:1
	THF/HMPA	20°C	1 min.	-78°C	71%	15.5:1

a Aldehydes were kept at the indicated temperature for 5 min., and at room temperature for half an hour. b Isolated yields based on aldehydes. c The *Z/E* ratios of iodoolefins were determined by NMR and by capillary GC analysis, and the assignment of stereochemistry to the iodoolefins was easily made from the coupling constants of the vinyl hydrogens ($J_{(Z)}$= ~ 7.5 Hz; $J_{(E)}$= ~ 14 Hz).

To a suspension of iodomethyltriphenylphosphonium iodide[3] (0.55g, 1mmol in 2.3ml of THF) at room temperature was slowly added 1ml of a 1M solution of sodium hexamethyldisilazane in THF. After stirring for 1 min., the solution was cooled to -60 °C, and HMPA (0.3ml) was then added, followed by cooling to -78 °C and addition of cyclohexanecarboxaldehyde (0.1ml, 0.8mmol). The cold bath was removed, and stirring was continued for 30 min.. Hexane (20ml) was added to the reaction mixture and, after the usual work up, column chromatography on silica gel gave (2-iodoethenyl)cyclohexane in 71% yield. The *Z/E* ratio of the olefins was 15.5/1, as determined by NMR and by capillary glc.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for financial support.

References and Notes

1 See: M. Gardette, N. Jabri, A. Alexakis and J. F. Normant, *Tetrahedron*, **40**, 2741 (1984).

2 See: K. Takai, K. Natta and K. Utimoto, *J. Am. Chem. Soc.*, **108**, 7408 (1986). An efficient synthesis of *E*-vinyl halides is, however, described in this paper.

3 D. Seyferth, J. K. Heeren, G. Singh, S. O. Grun and W. R. Hughes, *J. Organomet. Chem.*, **5**, 267 (1966). These workers describe the preparation of the phosphorane in small yield, admixed with a considerable quantity of the deiodinated methylenephosphorane.

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