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THE APPLICATION OF HIGH PRESSURE TO SOME DIFFICULT WITTIG REACTIONS

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Wittig reactions, previously shown to be favourably accelerated under pressure have been carried out between the stabilised ylides carboethoxymethylenetriphenylphosphorane and carboethoxyethylidinetriphenylphosphorane with a variety of ketones at 9-10 kbar pressure. Successful formation of tri- and tetra-substituted ethylenes is reported.

We have previously measured volumes of activation of Wittig reactions and have shown that they are associated with moderate to large negative volumes of activation (between -20 to -30 $cm^3 mol^{-1}$) [1]. This is understandable since the mechanism is believed to comprise a rate-determining formation of a zwitterion intermediate and the reduction in volume is a combination of the effects of association of the reagents and solvation [2]. The observation suggests that high pressure conditions will be capable of extending the useful range of this most versatile synthesis of alkenes, and in particular making possible the preparation of tetra-substituted ethylenes [2]. We have therefore examined eighteen systems in order to explore the limitations of this approach. The Table sets out results,comparing yields at 1 bar and at 9 kbar. The products in all cases were the expected alkenes together with the equivalent amounts of triphenylphosphine oxide. New compounds had correct analytical and spectroscopic data.In all cases yields were much higher under pressure than at 1 bar which for some ketones was shown to be the only route to the product. This was the case for the steroidal ketones where 3-ketones proved more reactive than 17- . The technique promises well to be useful for the synthesis of tetra-substituted alkenes although a limitation was reached with the ethylidenphosphorane which failed to react with benzophenone at the pressure used. However, the logarithmic relationship between rate and pressure means that a further small increase in pressure could result in a very large rate increase so that even highly hindered ketones might eventually add to ylides of low reactivity.

Table

ketone	Reaction at 1 bar		Reaction at 9kbar		
	conditions	yield/%	T/°C	t/hours	yield%
A Ylide = $Ph_3P{=}CHCOOEt$;					
$Me_2C{=}O$	24hr reflux	15	35	24	75
$Et_2C{=}O$	xylene reflux	0	50	30	70
nPr.CO.Me	xylene,reflux	<40	50	30	96
PhCOMe	170°,10 hr	68	50	30	98
$Ph_2C{=}O$	reflux,24 hr	10	50	35	82
β -ionone	toluene reflux 2 days	<50	50	24	60
testosterone	benzene reflux 24 hr	0	50	30	22
			50	120	32
Δ^4-Androstene-3,17-dione[a]	"	0	50	24	22
			50	120	58
19-nortestosterone	"	0	50	24	25
Dehydroisoandrosterone -3-acetate	"	0	50	24	20
			50	120	32
4-Cholestene-3-one	"	0	50	24	30
			50	120	69
B Ylide = $Ph_3P{=}CHCOOtBu$;					
PhCOMe			50	24	70
$Ph_2C{=}O$			50	24	50
C Ylide = $Ph_3P{=}CMeCOOEt$;					
$Me_2C{=}O$	reflux 6hr	1	50	48	80
nPrCOMe	"	0	50	48	10
$Et_2C{=}O$	"	0	50	48	10
PhCOMe	"	0	50	48	25
PhCOPh			50	24	0

[a] reaction at 3-ketone only

References;

1 N.S.Isaacs and O.H.Abed, Tetrahedron Letters,27,995,(1986).

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3 I.Gosney and A.G.Rowley, 'Organophosphorus Reagents in Organic Chemistry' J.I.G.Cadogan (Ed.), Academic Press,London,(1979).

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