Pergamon

Tetrahedron Letters, Vol. 37, No. 8, pp. 1281-1284, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02374-7

Wittig Reactions in the Presence of Silica gel

Vijay J. Patil* and Ursula Mävers

Institute de Chimie Organique, Université de Lausanne, Rue du la Barre - 2, CH - 1005, Lausanne, Switzerland.

Abstract : Wittig reactions, of stable phosphorous ylids, when carried out in presence of silica gel, in hexane, provide a fast, efficient and simple method to obtain α : β unsaturated compounds in high yields and high purity.

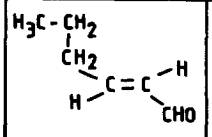
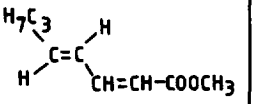
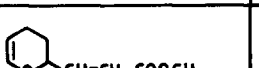
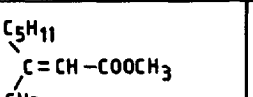
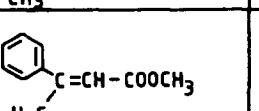
The Wittig reactions have been well investigated[1a,b,c]. It has been well documented[1d,e] in the literature that Wittig reactions of the stable ylids with aldehydes are much slower especially in non polar solvents and that they do not react with ketones under normal conditions. During the investigations of Wittig reaction[1f] we observed that certain reactions proceeded extremely fast in the presence of silica gel. Earlier investigations[2a-e] to increase the rate of reaction of the stable ylids have led to the realisation that additives like benzoic acid increase the rate of the reaction with aldehydes and also that ketones which are sluggish to react, readily undergo the Wittig reaction in the presence of catalytic amount of benzoic acid at elevated temperatures. However addition of benzoic acid involves an additional process of purification, along with the removal of triphenylphosphine oxide (formed in the reaction mixture) in the process of obtaining the product. Also it was observed that the reaction of aldehydes with resonance stabilized ylids gets strongly accelerated when the reactions are carried out at about 10 kbar pressures[2f]. Remarkable rate enhancements and dramatic reductions of reaction times in the Wittig reactions were observed[3] when a mixture of triphenylcarbethoxymethylene phosphorane, an aldehyde and silica gel (200 - 300 mesh) was irradiated in a microwave oven for 5-6 minutes. This enhancement in the rate of Wittig reaction is clearly due to microwave heating as when a similar experiment carried out with the ylid adsorbed on silica gel, however without microwave irradiation, does not show any enhancement in the rate of the reaction (see summary of our results). In this case[3] only aromatic aldehydes have been studied and furthermore the reaction mixture has to be chromatographed to obtain the product.

Following our observations during our investigations[1f] we decided to investigate the efficacity of silica gel as additive in Wittig reactions, of stable ylids, with aldehydes and ketones, in hexane. It is well known that triphenylphosphine oxide is soluble in most of the polar solvents and is very little soluble in hexane. However the reactions of stable ylids are very sluggish in hexane (see table). A survey of literature indicated that so far there have been no investigations of Wittig reactions in the presence of silica gel. Our rationale behind this exercise was that -- silica gel should increase the rate of the reaction, should help to remove the triphenylphosphine oxide formed in the reaction so that the product formed could be obtained in high yield and of high purity and thereby eliminating the need of further purification. Furthermore silica gel can be removed from the reaction mixture simply by filteration. Reactions of the stable ylid

---

*Present address: Fine Chemicals Lab., Division of Organic Chemistry-III, Indian Institute Of Chemical Technology , Hyderabad, India 500 007.

$Ph_3\overset{+}{P} - \bar{C}H - COOCH_3 + (A) \xrightarrow[25°C]{\text{Hexane}} \text{PRODUCT}$

(A)	HEXANE + ((A) + SiO_2)			HEXANE + (A)			PRODUCT	Ref.
	Time[a] (h)	Z : E[b]	Yield[c] (%)	Time[a] (h)	Z : E[b]	Yield[c] (%)		
$H_7C_3 - CHO$	2	10 : 90	87	42	9 : 91	89	H_7C_3-CH=CH-$COOCH_3$	5
$(H_3C)_2$-CH-CHO	2	18 : 82	84	54	4 : 96	86	$(H_3C)_2$-CH-CH=CH-$COOCH_3$	6
$(H_3C)_3$-C-CHO	6	27 : 73	78	144	7 : 93	42	$(H_3C)_3$-C-CH=CH-$COOCH_3$	7
	6	14 : 86	85	168	18 : 82	87		8
	2	12 : 88	90	60	5 : 95	90		9
	< 1	7 : 93	90	12	5 : 95	90		5
H_3CO-CH - CHO	< 3	18 : 82	85	3	18 : 82	85	H_3CO-CH_2-CH=CH-$COOCH_3$	10
	< 1	32 : 68	85	10	28 : 72	83		11
H_3C-$(CH_2)_4$-C(=O)-CH_3	> 100	30 : 70	5	> 100	—	—		12
	> 100	37 : 63	5	> 100	—	—		13

a) Maximum consumption of (A) b) determined by GC c) of pure isolated products

Triphenylphosphinomethoxycarbonyl methanide, with various aldehydes and ketones, in the presence of silica gel, in hexane as solvent and at room temperature were carried out. At the same time similar reactions with the same stabilized ylid, in hexane, however without silica gel, were carried out for comparison. The results obtained from these experiments are presented in the table and could be summarised as follows :

a) the reactions of the ylid with aldehydes adsorbed on silica gel are rapid.

b) the products are obtained in high yields. The yields are slightly higher in case of the reactions without silica gel. In in case of pivalaldehyde the yields are almost double, when the reaction is carried out in the presence of silica gel.

c) no additional purification is necessary to remove the triphenylphosphine oxide, a simple filteration (see general procedure) is sufficient to provide a product of high purity.

d) there is a decrease in *trans* selectivity in case of aliphatic aldehydes as the substitution on the α carbon atom of the aldehyde increases.

e) sterically hindered aldehydes also react very well.

f) there is no reaction with ketones even after 100 h. A trace (5%) of product was observed in case of reaction in the presence of silica gel after 100 h.

g) under microwave irradiation[3] the ylid on silica gel reacted very well with aldehyde on silica gel, however in our case the reaction was extremely sluggish when the ylid adsorbed on silica gel was reacted with the aldehyde in solution. This clearly indicates that the microwaves help in the former case.

h) any commercial grade silica gel (60 -120 mesh) can be used for the Wittig reactions.

i) Although reactions of only one stable ylid has been reported in this communication the other stable ylids show similar behavior, details of which will be published in due course of time.

The surface of silica gel itself is mildly acidic and it has been observed[4] that silica gel accelerates reactions catalysed by weak acid. The acceleration observed in case of Wittig reactions could be possibly due to this weak acidity of silica gel.

General procedure :

a) for silica gel containing reactions : to a dry schlenk tube, flushed with nitrogen, was added commercial grade silica gel (three times the weight of aldehyde or ketone) followed by the aldehyde or ketone (30 mmol). The resulting mixture was stirred for 5 min. so as to obtain a free flowing powder, hexane (80 mL) was added followed by the ylid (36 mmol). The resulting mixture was stirred at 25 °C.

b) reactions without silica gel : to a dry schlenk tube flushed with nitrogen were added successively ylid (36 mmol), hexane (80 mL) and aldehyde or ketone (30 mmol) and the resulting mixture stirred at 25 °C.

The reactions were monitored by GC at regular time intervals (Carbowax C20M / 5%-2m*) and the time when the minimal concentration (less than 1%) of the starting material was observed has been noted in the table.

Workup : the reaction mixture was filtered through a pad of silica gel (4 cms. thick) and the residue washed with 100 ml of a mixture ethyl acetate : hexane (1 : 20). The solvent from the combined filterates was distilled off / evaporated under reduced pressure to obtain the products.

The cis : trans mixtures were seperated by preparative GC (Carbowax C20M / 8% -2m*) to obtain pure cis and trans products. The cis : trans ratios were established by comparing the product ratios on two columns of GC - 1) Carbowax C20M / 5% - 2m* and 2) SE - 30 / 5% - 2m*.

Olefins : Methyl 2-hexenoate[5]: *cis Isomer*: bp 148-151 °C/760 mmHg; n_D^{20} 1.4311. *trans Isomer*: bp 153-155 °C/760 mmHg; n_D^{20}1.4342. **Methyl 4-methyl-2-pentenoate**[6]: *cis Isomer*: bp 150-152 °C/760 mmHg; n_D^{20} 1.4251. *trans Isomer*: bp 154-156 °C/760 mmHg; n_D^{20} 1.4340. **Methyl 4,4-dimethyl-2-pentenoate**[7]: *cis Isomer*: bp 155-157 °C/760 mmHg; n_D^{20} 1.4291. *trans Isomer*: bp 160-162 °C/760 mmHg; n_D^{20} 1.4350. **Methyl 2,4-octadienoate**[8]: *cis Isomer*: bp 190-192 °C/760 mmHg; n_D^{20} 1.4921. *trans Isomer*: bp 201-203 °C/760 mmHg; n_D^{20} 1.4978. **Methyl 3-cyclohexyl-2-propenoate**[9]: *cis Isomer*: bp 210-212 °C/760 mmHg; n_D^{20} 1.4710. *trans Isomer*: bp 219-222 °C/760 mmHg; n_D^{20} 1.4760. **Methyl 3-phenyl-2-propenoate**[5]: *cis Isomer*: bp 230-232 °C/760 mmHg; n_D^{20} 1.555. *trans Isomer*: mp 35-36 °C. **Methyl 4-methoxy-2-butenoate**[10]: *cis Isomer*: 145-148 °C/760 mmHg; n_D^{20} 1.4344. *trans Isomer*: 152-154 °C/760 mmHg; n_D^{20} 1.4396. **(R,S) Methyl 3-[2',(3',4')dihydropyranyl]-2-propenoate**[11]: *cis Isomer*: bp 54-56 °C/0.65 mmHg; n_D^{20} 1.4789 . *trans Isomer*: bp 64-66 °C/0.65 mmHg; n_D^{20} 1.4847. **Methyl 3-methyl-2-octenoate**[12]: *cis Isomer*: bp 195-198 °C/760 mmHg; n_D^{20} 1.4479. *trans Isomer*: bp 208-210 °C/760 mmHg; n_D^{20} 1.4507. **Methyl 3-phenyl-2-butenoate**[13]: *cis Isomer*: mp 16-18 °C. *trans Isomer*: mp 33-35 °C.

Acknowledgement : The authors are indebted to the Swiss Science Foundation for financial support (Grant 20 - 29'838 - 90) to Prof. Manfred Schlosser.

References :

1. a. Maerckar, A. *Organic reactions*,**1965**, *14*, 270. b. Schlosser, M. *Topics Stereochem.* **1970**, *5*, 1. c. Maryanoff, B. E. ; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. d. Wittig, G. ; Haag, W. *Chem. Ber.***1955**, *88*, 1654. e. Kucherov, V. F. ; Kovalev, B. G.; Nazarova, I. I. ; Yanovaskaya, L. A. *Izv. Akad. Nauk. S.S.S.R, Otdel. Khim. Nauk.* **1960**, 1512. *Chem. Abstr.* **1961**, *55*, 1420b. f. Patil, V. J. ; Schlosser, M. *Synlett.* **1993**, 125.
2. a. Rüchardt, C. ; Eichler, S. ; Panse, P. *Angew. Chem.* **1963**, *75*, 858. b. Rüchardt, C. ; Eichler, S. ; Panse, P. *Angew. Chem. Int. Ed. Eng.* **1963**, *2*, 619. c. Rüchardt, C. ; Panse, P. ; Eichler, S. *Chem. Ber.* **1967**, *100*, 1144. d. Fliszar, S. ; Hudson, R., F. ; Salvadori, G. *Helv. Chem. Acta.* **1964**, *47*, 159. e. Bose, A. K. ; Manhas, M. S. ; Ramer, R. M. *J. Chem. Soc.* (C) **1969**, 2728. f. Nonnenmacher, A. ; Mayer, R. ; Plieninger, H. *Liebigs Ann. Chem.* **1983**, 2135.
3. Xu, C. ; Chen, G.; Fu, C.; Huang, X. *Synth. Comm.* **1995**, *25*, 2229.
4. Kropp, P. J. ; Breton, G. W. ; Craig, S. L. ; Crawford, S. D. ; Durland, Jr., W. F. ; Jones, III, J. E. ; Raleigh, J. S. *J. Org. Chem.* **1995**, *60*, 4146; and references cited therein.
5. Bestmann, H. J. ; Dörnauer, H. ; Rostick, K. *Chem. Ber.* **1970**, *103*, 685.
6. McGreer, D. E. ; Chiu, N. W. K. *Can. J. Chem.* **1968**, *46*, 2225.
7. Wilson, J. W. ; Stubblefield, V. S. *J. Am. Chem. Soc.* **1968**, *90*, 3423.
8. Still, W. C. ; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
9. Metzger, J. O. ; Henke, K.; Hartmanns, J. ; Eisermann, D. *Chem. Ber.* **1986**, *119*, 508.
10. Harding, K. E. ; Clement, B. A. ; Moreno, L. ; Peter-Katalinic, J. *J. Org. Chem.* **1981**, *46*, 940.
11. Büchi, G. ; Powell, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 3126.
12. ^{1}H-NMR ($CDCl_3$) : *cis isomer*: 5.7 (1H, m), 3.69 (3H, s), 2.6 (2H, m), 1.91 (3H, d, *J* 1.3), 1.4 (6H, m), 0.91 (3H, t, *J* 7.2). *trans isomer*: 5.66 (1H, ddq, *J* 2.5, 1.2, 1.0), 3.69 (3H, s), 2.16 (3H, d, *J* 1.2), 2.10 (2H, ddd, *J* 7.2, 2.5, 1.0), 1.47 (2H, pent., *J* 7.2), 1.3 (4H, m), 0.90 (3H, t, *J* 7.2).
13. Abley, P. ; McQuillin, F.J. *J. Chem. Soc.* (C) **1971**, 844.

(*Received in UK* 4 *October* 1995; *revised* 12 *December* 1995; *accepted* 15 *December* 1995)