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**CHEMISTRY OF THE WITTIG REACTION.  
THE ROLE OF HARD, SOFT AND BORDERLINE BASES  
IN WITTIG CONDENSATION APPLIED  
IN PHEROMONE CHEMISTRY**

*(Presented by Ü. Lille)*

Formation of the C—C double bond represents the main problem in the synthesis of unsaturated pheromone compounds. To solve this problem the Wittig condensation offers an excellent possibility [1–5].

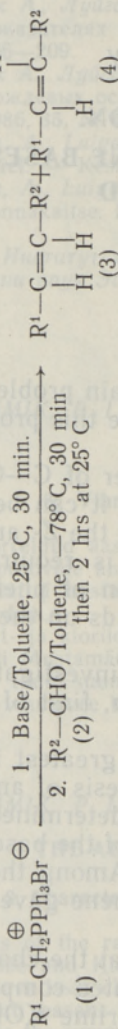
The Wittig reaction never gives totally pure *Z*-isomer of C—C double bond in the case of aliphatic reactants [6]. Nevertheless it can be applied well in the synthesis of pheromones, where a mixture of the *Z*- and *E*-isomers, containing mainly the former one (90–98%), is required. This method can be applied even for large scale preparation of pheromones, though the success of the whole synthesis greatly depends on the yield of the condensation.

In this paper we wish to report on our recent investigation and findings which correlate the yield of the Wittig reaction, first of all with the type of base applied for the ylid generation.

In fact, the structure of the reactants possesses the greatest influence on the yield of the Wittig reaction. In a multistep synthesis of an unsaturated compound, however, this factor is usually well determined by the target molecule. Among the reminding factors the role of the base and the solvents applied were found the most important ones. Among the aprotic solvents suitable for the Wittig reaction, THF and toluene gave the best results. Less or more polar solvents decreased the yield.

Systematic experiments unambiguously pointed out that the character of the base influences significantly the yield of an unsaturated compound. As hard base sodium and potassium alcoholates, as borderline  $\text{KOBU}^t$  were applied,  $\text{BuLi}$ ,  $\text{NaHMDS}$  and  $\text{K/HMPT}$  can be regarded as soft ones. Hard bases were found to ensure the best results; lower yields were obtained when borderline bases were applied, and finally soft bases afforded the poorest results (Table 1). The phenomenon observed could be explained by the HSAB principle [7–12]. Hard bases attack at room temperature predominantly the  $\alpha$ -hydrogen (hard center) of the phosphonium salt, thus resulting the desired ylid. Borderline bases are able to react also with the soft phosphor atom and/or the H atom of the benzene ring in small amounts. Soft bases can attack three sites of the phosphonium compound in comparable amounts, thus consuming it in side reactions (Table 2) [13–15].

## Results of the Wittig condensation



Entry	R <sup>1</sup>	R <sup>2</sup>	BASE <sup>a</sup>									
			n-BuLi		NaHMDS		K/HMPA		KOBut		NaOEt <sup>b</sup>	
			A <sup>c</sup>	B <sup>c</sup>	A <sup>c</sup>	B <sup>c</sup>	A <sup>c</sup>	B <sup>c</sup>	A <sup>c</sup>	B <sup>c</sup>	A <sup>c</sup>	B <sup>c</sup>
1.	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>7</sub> -	50	80:20	30	90:10	30	90:10	60	90:10	80	90:10
2.	HO-(CH <sub>2</sub> ) <sub>4</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	35	80:20	40	96:4	40	95:5	60	98:2	80	95:5
3.	CH <sub>3</sub> OOC-(CH <sub>2</sub> ) <sub>3</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	30	80:20	20	95:5	15	94:6	50	95:5	60	90:10
4.	CH <sub>3</sub> -CH <sub>2</sub> -	CH <sub>3</sub> OOC-(CH <sub>2</sub> ) <sub>9</sub> -	20	80:20	20	97:3	18	94:6	30	98:2	50	94:6
5.	CH <sub>3</sub> OOC-(CH <sub>2</sub> ) <sub>9</sub> -	CH <sub>3</sub> -CH <sub>2</sub> -	45	80:20	45	97:3	30	95:5	60	97:3	70	95:5
6.	HO-(CH <sub>2</sub> ) <sub>6</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	40	80:20	45	97:3	35	93:7	60	98:2	70	96:4
7.	CH <sub>3</sub> OOC-(CH <sub>2</sub> ) <sub>8</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	50	80:20	50	98:2	35	95:5	70	98:2	80	94:6
8.	AcO-(CH <sub>2</sub> ) <sub>2</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -CH=CH-(CH <sub>2</sub> ) <sub>8</sub> -	35	80:20	30	98:2	20	94:6	40	98:2	50	92:8
9.	CH <sub>3</sub> OOC-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	40	80:20	40	98:2	30	98:2	60	98:2	80	95:5
10.	CH <sub>3</sub> OOC-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>3</sub> -	30	80:20	30	97:3	20	97:3	50	97:3	60	94:6

SOFT BASES

BORDERLINE  
BASEHARD  
BASE

*a* — NaHMDS (NaH is dissolved in HMDS), K/HMPA (K is dissolved in HMPA) and NaOEt (Na is dissolved in EtOH) were prepared *in situ* and after distilling off the side products the bases were dissolved in toluene. KOBut was prepared by dissolving potassium in the mixture of *t*-BuOH (4 equiv.)-toluene (1:4) and after total solvation of the K the excess of *t*-BuOH was removed by distillation together with toluene. A solution of KOBut in toluene was obtained which was used for the Wittig condensation.

*b* — NaOMe, KOEt and KOMe gave the same results.

*c* — A: Yield of (3) + (4), %

The base-sensitive groups of (1) and (2) can produce number of side reactions (for example see [17] and [18]), which moderate the yield of (3) + (4).

B: Ratio of (3) and (4) (*Z/E*).

The ratio of (3) and (4) were determined by GC analysis which were made by Perkin Elmer F22 instrument with

*a*: CPSIL 5CB (50 m×0.22 mm i. d., df=0.15 μm),

*b*: CPWAX 57CB (25 m×0.22 mm i. d.) capillary columns and FID detector (*T* of detector and injector 200 °C), carrier: N<sub>2</sub>, 2.7 ml/min, split 1:100, make-up 20 ml/min.

Retention times: (entry: 3 (min)/4 (min), (*T*<sub>column</sub> (°C), type of column)).

1: 25.9/26.3 (90, *a*); 2: 81.3/82.1 (90, *a*); 3: 51.2/51.9 (90, *a*); 4 and 5: 5.94/5.73 (160, *b*); 6: 10.29/9.78 (160, *b*); 7: 12.72/12.48 (150, *b*); 8: 31.2/31.8 (180, *a*); 9: 18.6/18.4 (140, *b*); 10: 10.1/9.9 (130, *b*).

## Experimental

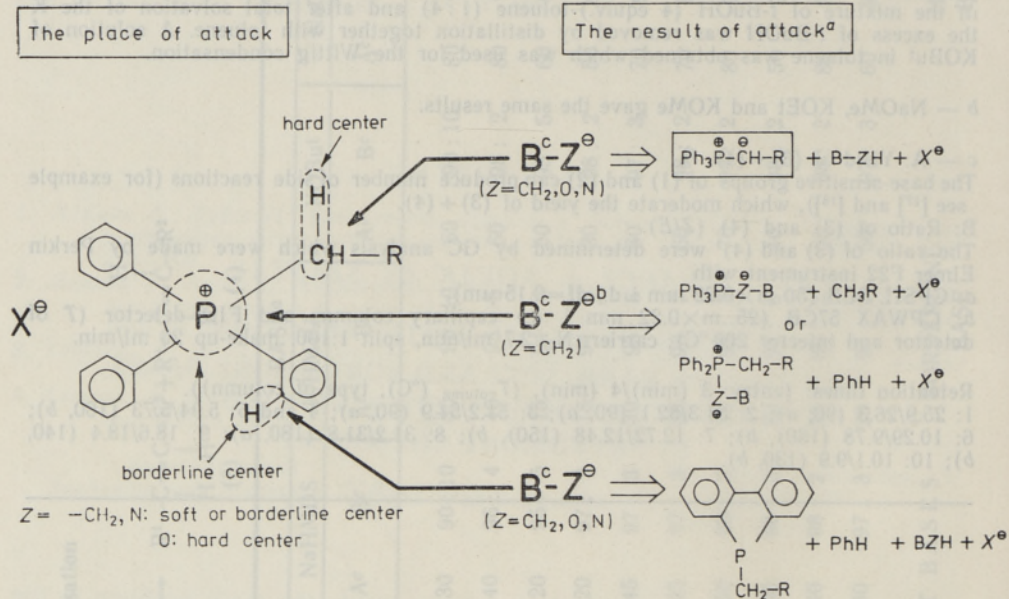
Satisfactory IR, <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were determined for all new compounds. (These results are under publication.) The intermediates and products were purified using dry column flash chromatography (DCFC) [19, 20].

**Preparation of phosphonium salts (1).** Phosphonium salts (1) were prepared by refluxing of the appropriate bromide (1.0 equiv.) and PPh<sub>3</sub> (1.0 equiv.) in CH<sub>3</sub>CN (2 ml/g of PPh<sub>3</sub>) for 24 hrs. The reaction mixture was concentrated in vacuum after cooling and the white precipitate was filtered off and washed with benzene and ether.

**Preparation of aldehydes (2).** All aldehydes were prepared by oxidation of appropriate alcohol using PCC [21] or activated DMSO [22].

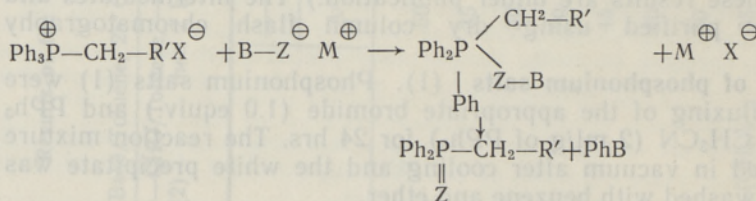
**General method for the Wittig condensation.** (1) (1.1 equiv.) was added to a solution of base (1.1 equiv.) in toluene (100 ml/g of (1)) and stirred for 30 min at 25 °C. The side products formed were distilled off with toluene in high vacuum and the residue was diluted to the original concentration by toluene. The resulting solution was cooled to -78 °C and a solution of aldehyde ((2); 1.0 equiv.) in toluene (1 ml/g of (2)) was added. The mixture was stirred for 30 min at -78 °C and then for 2 hrs at 25 °C. After quenching with cold and saturated NH<sub>4</sub>Cl (60 ml/g of base) the mixture was extracted with hexane, the organic extract was washed with saturated NH<sub>4</sub>Cl, 5% NaHCO<sub>3</sub>, water and brine. After drying (Na<sub>2</sub>SO<sub>4</sub>) the solution was concentrated and the residue purified by DCFC [19, 20].

## Interaction of bases with phosphonium salt



<sup>a</sup> — see [13–15].

<sup>b</sup> — in case of alkoxide type base (Z=O<sup>⊖</sup>) another side reaction is under investigation:



If B=H, this reaction is well known [16]. Now we are investigating the cases when B=Me, Et, Bu<sup>t</sup>.

<sup>c</sup>

Base	B	Z <sup>⊖</sup>
<i>n</i> -BuLi	C <sub>3</sub> H <sub>7</sub> -	CH <sub>2</sub>
NaHMDS	(Me <sub>3</sub> Si) <sub>2</sub>	N
K/HMPA	(Me <sub>2</sub> N) <sub>2</sub> PN-    O	CH <sub>2</sub>
KOBu <sup>t</sup>	But-	O
NaOEt	Et-	O

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#### WITTIGI REAKTSIOONI KEEMIA.

#### JÄIGA, PEHME JA PIIRDALUSE ROLL WITTIGI KONDENSATSIOONIS RAKENDATUNA FEROMOONIDE KEEMIAS

On esitatud rea alifaatsete ühendite Wittigi järgi olefiinimise tulemused, mis sõltuvad mitmesugusest aluseist. Tulemusi on tõlgendatud jäiga—pehme aluse kontseptsiooni seisukohalt. Kirjanduse andmeid üldistades on näidatud jäiga aluse sobivust olefiini kõrge saagise saamisel.

П. ВИНЦЕР, З. ЮВАНЦ, Л. НОВАК, Ч. САНТАЙ

#### ХИМИЗМ РЕАКЦИИ ВИТТИГА.

#### РОЛЬ ЖЕСТКОГО, МЯГКОГО И ГРАНИЧНОГО ОСНОВАНИЙ В РЕАКЦИИ ВИТТИГА, ПРИМЕНЕННОЙ В ХИМИИ ФЕРОМОНОВ

В статье представлены результаты olefiinimise по Виттигу ряда алифатических соединений в присутствии различных оснований. Результаты интерпретируются по концепции жестко-мягких оснований и, путем обобщения литературных данных, показывается предпочтение жесткого основания для получения высокого выхода olefiina.