Tetrahedron Vol 43, No. 3, pp. 537 to 542, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

KNOEVENAGEL, WITTIG AND WITTIG-HORNER REACTIONS IN THE PRESENCE OF MAGNESIUM OXIDE OR ZINC OXIDE.

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(*Received in France* 3 *December* 1986)

Abstract - *Alkenes are prepared by Wittig, Knoevenagel and Wittig-Horner reactions in solid-liquid systems, with magnesium oxide or zinc oxide as catalyst. When Wittig-Horner reaction is competitive with Knoevenagel reaction, the catalyst can be modified to give a highly selective reaction : the addition of dimethylsulfoxide on MgO or hexamethylphosphoric triamide on ZnO gives more efficient catalysts for the Wittig-Horner reaction. The addition of a small amount of* $HgCl_2$ *or* $CdCl_2$ *on ZnO gives more efficient catalysts for the Knoevenagel reaction.*

Reactions in heterogeneous media are known to be often more selective than in homogeneous solutions, with an easier isolation of the products. Knoevenagel reactions [1], Wittig [2,6] and Wittig-Horner [2-5] reactions have been performed with a solid catalyst such as alumina, potassium hydroxide, potassium carbonate, alumina supported potassium fluoride or barium hydroxide. Organic reactions involving magnesium oxide [7-9] or zinc oxide [10,11] have attracted the attention of organic chemists in the last few years. In an effort to develop selective metal oxide reagents, we have studied the abilities of magnesium oxide and zinc oxide to promote the synthesis of olefins from aldehydes. We have also examined the relationship between the addition of a small amount of protic or aprotic solvent or metal salts to the metal oxides on the selectivity of the reaction of benzaldehyde with diethyl cyanomethylphosphonate.

Results

The Wittig reaction. The reaction of aldehydes with phosphonium salts was carried out in the presence of MgO or ZnO (equation (1)).

$$\underset{\mathbf{1}}{R^1CHO} \; + \; \underset{\mathbf{2}}{R^2CH_2\overset{+}{P}Ph_3,\ Cl^-} \; \xrightarrow{-HCl} \; \underset{\mathbf{3}\ (Z + E)}{R^1CH{=}CHR^2} \; + \; OPPh_3 \qquad (1)$$

When MgO was used, the addition of a limited amount of water was necessary to increase the reaction yield (table I). The yield of **3** was greatest with 4 g of water for 5 g of MgO. The addition of water to ZnO had no significant effect.

The Knoevenagel reaction. The Knoevenagel reaction of **1** with **4a-c** (reaction 2) was performed in the presence of MgO or ZnO, at room temperature (tables II and III).

$$R^1\text{—CHO} + \text{NC—CH}_2\text{—X} \longrightarrow R^1\text{—CH=C(X)CN} + H_2O \quad (2)$$

1 — **4a**, X = CN; **4b**, X = CO_2Me; **4c**, X = $CONH_2$ — **5a-c** (E)

The addition of a small amount of water on MgO decreased the yield of alkene. Poor yields were obtained when dry ZnO (Zn + O_2) was used as catalyst. ZnO (Zn + O_2) has a low surface area (5 m^2/g) and contains very small amounts of water (see experimental section). The addition of a limited amount of water or polar organic solvent to ZnO (Zn + O_2) increased the yield (table III). ZnO prepared by drying $Zn(OH)_2$ gave 100 % yield of **5b** under the same conditions as table III. This zinc oxide has a surface area of 18 m^2/g and contains 1.5 % of water by weight.

Table I - Wittig reaction in the presence of MgO or ZnO

Aldehyde **1** R^1	Phosphonium salt **2** R^2	Solid base	Time h	Temp. °C	Yield of **3**[a] %	Product molar ratio **3** Z / **3** E	M.p[°C] or B.p[°C]/Torr	Ref
Ph	CN	MgO[b]	2	20	87[e]	40/60	90/0.03	15
iPr	CN	MgO[b]	24	20	32	20/80	154/754	19
$pClC_6H_4$	CN	MgO[b]	4	60[c]	65	35/65	78	18
Ph	CO_2Et	MgO[b]	4	20	79	10/90	100/0.03	15
$pClC_6H_4$	CO_2Et	MgO[b]	4	60[c]	60	12/88	110/0.03	16
Ph	Ph	MgO[b]	24	20	30	60/40[d]	124	17
Ph	CN	ZnO	24	20	80	30/70	90/0.05	15
Ph	Ph	ZnO	24	20	25	50/50[d]	124	17

[a]Isolated product. [b] 4 g of water were added to MgO (5 g). [c] The aldehyde is liquid at this temperature. [d] Calculated by g.l.c. analysis. [e] 2 g of water/5 g MgO : 67 % of **3** ; 6 g of water/5 g MgO : 74 % of **3**.

Table II - MgO catalyzed Knoevenagel reaction, at 20°C

Aldehyde **1** R^1	$NCCH_2X$ **4** X	Time (min.)	Yield of **5**[a] %	M.p[°C] or B.p[°C]/Torr	Ref
Ph	CN	5	94	82	20
Ph	CO_2Me	30	94	90	21
Ph	$CONH_2$	200	60	123	22
	CN	5	96	72	23
	CO_2Me	5	96	95	24
$pClC_6H_4$	CN	10	91	162	25
iPr	CN	10	93	20/0.03	26
iPr	CO_2Me	30	93	50/0.03	27
Acetone	CN	10	40	50/0.03	28

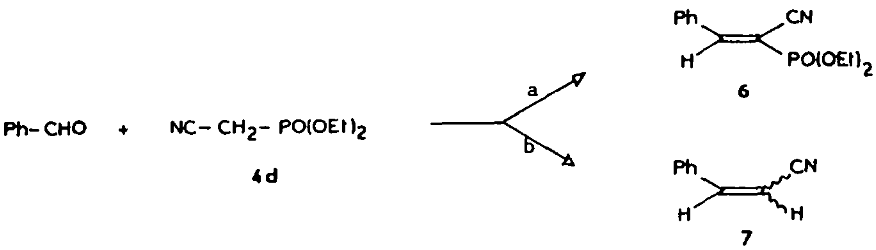
[a] Isolated pure product **5**.

Table III - Solvent effect (25 mmol of solvent) on 4 g of ZnO ($Zn + O_2$) for the reaction of PhCHO with **4b** at 20°C (5 h).

Solvent	without	C_5H_{12}	MeCN	THF	DMF	DMSO	H_2O[b]	MeOH
Yield of **5b** (%)[a]	15[c]	20	20	30	100	100	40[c]	94

[a] Estimated by NMR. [b] the highest yield of 5 (60 %) was obtained with 125 mmol of water on 4 g of ZnO. [c] When the reaction time was lengthened, the yield of **5b** was increased.

Competition between Wittig-Horner reaction and Knoevenagel reaction. The reaction of diethyl cyanomethylphosphonate **4d** with PhCHO gave cinnamonitrile **7** (Wittig-Horner reaction (3b)) and alkene **6** (Knoevenagel reaction (3a)). The **7**/**6** ratio was dependant on the catalyst (MgO or ZnO) and the addition of protic or dipolar aprotic solvents or metal salts (tables IV and V).



(3)

Table IV - Effect of added solvent or metal salts on the selectivity of the reaction of PhCHO with **4d** catalyzed by MgO[a].

Reagent (mmol for 4 g of MgO)	Product distribution[c] 6 (%)	7 (%)[b]	Overall yield (%)[c]
none	30	70	95
H_2O (10)	10	90	97
DMF (5)	15	85	93
DMSO (10)	5	95	95
$HgCl_2$ (10)	80	20	93
$CdCl_2$ (10)	90	10	90

[a] Reaction conditions : 20°C, 24 h. [b] E/Z = 40/60. [c] Estimated by NMR.

Table V - Effect of added solvent or metal salts on the selectivity of the reaction of PhCHO with **4d** catalyzed by ZnO ($Zn + O_2$)[a].

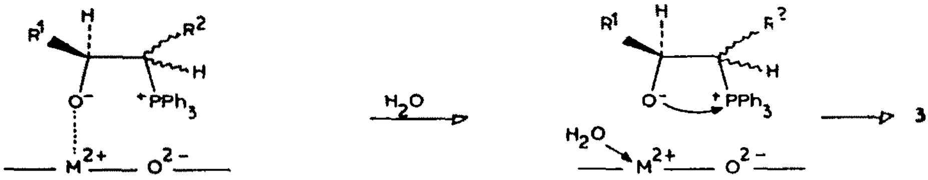
Reagent (mmol for 4 g of ZnO)	Product distribution[c] 6 (%)	7 (%)[b]	Overall yield (%)[c]
none	84	16	97
H_2O (10)	85	15	89
MeOH (10)	80	20	93
MeCN (10)	80	20	95
DMF (10)	50	50	95
DMSO (10)	30	70	95
HMPA (10)	0	100	95
KCl (5)	60	40	98
$Al_2(SO_4)_3$	80	20	90
$MgCl_2$ (5)	90	10	97
$MnSO_4$ (2)	93	7	94
$HgCl_2$ (5)	> 96	< 4	96
$CdCl_2$ (5)	> 96	< 4	92

[a] Reaction conditions : 50°C, 24 h. [b] E/Z - 30/70. [c] Estimated by NMR.

Discussion

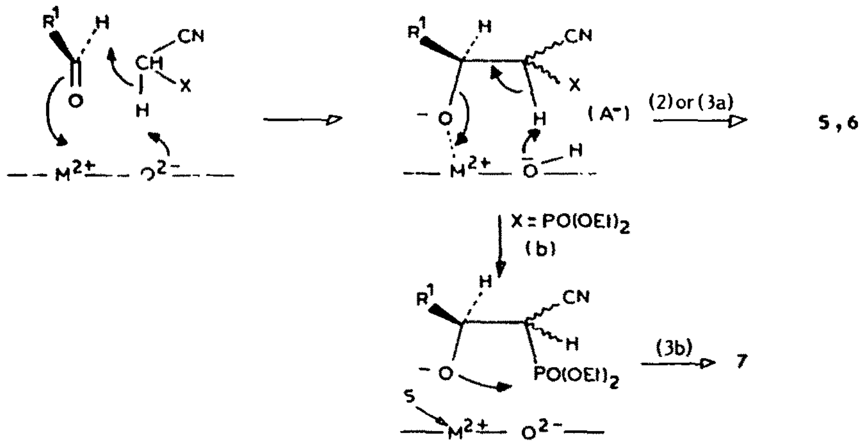
Both acidic and basic sites on the surface of the catalyst are considered to work synergistically on substrates to promote the reactions.

Magnesium oxide and zinc oxide are basic enough to yield the phosphonium ylide (reaction (1)). The addition of the ylide to the carbonyl compound gives a phosphonium betaine intermediate complexed with the metal cation. We have assumed that the tendency of the cation to coordinate with oxygen of the betaine is stronger for Zn^{2+} than for Mg^{2+}, and the displacement of the betaine by water is easier for Mg^{2+} than for Zn^{2+}. These assertions are in agreement with the relative stabilities of magnesium and zinc salts of carboxylic acids and with the stabilities of $MgOH^+$ and $ZnOH^+$ species.[12] Consequently, the betaine intermediate could be more easily desorbed from one MgO surface than from the ZnO surface by addition of water. As a result, the addition of a small amount of water on MgO accelerates the Wittig reaction, but has less effect with ZnO (scheme I).



Scheme I

The first step of reactions (2) and (3) is proton abstraction from compounds 4a-d and addition of the carbanion to the carbonyl group, to give the intermediate oxyanion A^- which is complexed with the cation of the metal oxide (scheme II).



Scheme II

Zinc oxide is less basic than magnesium oxide. Thus, the formation of A^- in the presence of ZnO is slow at room temperature. The selective solvation of Zn^{2+} by addition of a small amount of a dipolar aprotic solvent could induce the localization of electrons on oxygen atoms. This would result in an increased basicity of the solid base.[9] This would explain the acceleration of the Knoevenagel reaction by addition of DMF or DMSO on ZnO (table III). Addition of a protic solvent causes solvation of the cation and also the oxygen anion, especially in the case of water which is more acidic than methanol. Consequently, water is less able to increase the basic strength of the catalyst than the aprotic solvents.

The second step of the Knoevenagel reaction is the abstraction of the proton from the complex A^-/M^{2+} and cleavage of the carbon-oxygen bond (scheme II, path (2)). This cleavage is assisted by the complexation with the metal cation. The complex A^-/Mg^{2+} which is less stable than A^-/Zn^{2+}, can be easily destroyed by water. So, addition of water on MgO disfavours the Knoevenagel reaction.

With **4d**, Wittig-Horner reaction (3, path (b)) competes with Knoevenagel reaction (3, path (a)). The values listed in tables III and IV show that (b) is more favoured with MgO than with ZnO. The tendency of Mg^{2+} to coordinate the oxyanion being low, the attack of the oxygen on the phosphorus atom to give 7 is easy. The effect of the added solvent is low (table IV). When an aprotic solvent (DMF, DMSO or HMPT) is added to ZnO, the solvation of the metal cation displaces the intermediate compound A^- and promotes the Wittig Horner reaction. When a protic solvent is added, the anion A^- is again solvated, which does not favour the Wittig-Horner reaction (table V).

The addition of a metal salt can modify the surface properties of the oxides.[9] Particularly, the added metal ions form additional acidic sites which are able to give relatively stable complexes with the oxyanion A^-. This is the case with Mn^{2+}, Cd^{2+} and Hg^{2+} (tables IV, V). Then, Wittig-Horner reaction is inhibited and Knoevenagel reaction predominates.

Our investigations indicate the importance of the presence of a small amount of a polar solvent or a metal salt on the reactivity of MgO or ZnO.

Experimental section

Melting points are uncorrected. IR spectra were recorded as suspensions in nujol with a Perkin Elmer 225 spectrometer. ^1H NMR were recorded in $CDCl_3$ on a Bruker WP 80 CW instrument.

Solid catalysts. Zinc oxide ($Zn + O_2$) is the commercially available product. Zinc oxide can also be prepared by drying $Zn(OH)_2$. Zinc dihydroxide was obtained by addition of NaOH (40 g in 200 ml of water) to a solution of zinc nitrate (130 g in 2 l of water). The precipitate was filtered and dried under reduced pressure (0.02 torr) at 50°C during 12 h.

Magnesium oxide is the commercial product.

The amounts of water contained in the solid catalysts were measured by a thermogravimetric method.

ZnO ($Zn + O_2$) : 0.3 % of water by weight
ZnO (from $Zn(OH)_2$) : 1.5 + 0.1 % of water by weight
MgO : 5 % of water by weight.

Solid catalysts doped with metallic salts. A suspension of the salt (tables IV and V) and the solid catalyst (4 g) in ethanol (40 ml) was stirred during 5 min. The solvent was then evaporated under reduced pressure at 50°C. The residue was dried at 150°C under 0.02 torr during 12 h. The hydration of the catalysts was measured by a thermogravimetric method.

Wittig reaction (1). Solid catalyst (4 g) was added in small portions to the stirred equimolar mixture of aldehyde **1** and phosphonium salt **2** (10 mmol) (R^2 = CN[13], R^2 = CO_2Et, C_6H_5, $pClC_6H_4$[14]). The heterogeneous mixture was allowed to stand, at room temperature, during the appropriate time (table I). After addition of Et_2O, the mineral solid was eliminated by filtration. Ph_3PO was precipitated by addition of pentane to the etheral fraction. Evaporation of solvent under reduced pressure afforded olefin **3**, which was purified by short path distillation or recrystallisation.

Knoevenagel or Wittig-Horner reactions (2) and (3). Solid catalyst (4 g) was added to the equimolar mixture of 10 mmol of aldehyde **1** and compound **4a-d**. After appropriate reaction time (tables III, IV, V), the olefins **5**, **6** or **7** were extracted with CH_2Cl_2 (2 x 25 ml). Evaporation of CH_2Cl_2 afforded **5** with good purity.

Acknowledgement

The authors thank Mr. R. Prost, Institut National de la Recherche Agronomique, Versailles, for the determination of the surface areas and Mr. M. Matecki, Laboratoire de Chimie minérale, Université de Rennes, for the thermogravimetric measures.

References

1 - F. TEXIER-BOULLET and A. FOUCAUD, Tetrahedron Lett. 1982, **23**, 4927.
2 - F. TEXIER-BOULLET, D. VILLEMIN, H. MOISON and A. FOUCAUD, Tetrahedron, 1985, **41**, 1259 and references cited therein.
3 - J. VILLIERAS, M. RAMBAUD and B. KIRSCHLEGER, Phosphorus and Sulfur, 1983, **14**, 385.
4 - J.V. SINISTERRA, Z. MOULOUNGUI, M. DELMAS and A. GASET, Synthesis, 1985, 1097 and references cited therein.
5 - F. TEXIER-BOULLET and A. FOUCAUD, Synthesis, 1979, 884 ; Tetrahedron Lett. 1980, **21**, 2161.
6 - Y. LE BIGOT, M. DELMAS and A. GASET, Tetrahedron, 1986, **42**, 339. Y. LE BIGOT, R. EL GHARBI, M. DELMAS and A. GASET, Tetrahedron, 1986, **42**, 3813.
7 - R.M. MORRIS and K.J. KLABUNDE, Inorg. Chem. 1983, **22**, 682.
8 - M.F. HOQ and K.J. KLABUNDE, J. Am. Chem. Soc. 1986, **108**, 2114.
H.H. LAMB and B.C. GATES, J. Am. Chem. Soc. 1986, **108**, 81.
D.J. DRISCOLL, W. MARTIR, J.X. WANG, J.H. LUNSFORD, J. Am. Chem. Soc. 1985, **107**, 58.
9 - W. UEDA, T. YOKOYAMA, Y. MORO-OKA and T. IKAWA, Chem. Lett. 1985, 1059. J. Chem. Soc. Chem. Commun. 1984, 39.
10 - W.H. HIRSCHWALD, Acc. Chem. Res. 1985, **18**, 228.
11 - A.L. DENT, R.J. KOKES, J. Phys. Chem. 1969, **73**, 3781.
R.J. KOKES, Acc. Chem. Res. 1973, **6**, 226.
12 - L.G. SILLEN and A.E. MARTELL, Stability Constants of Metal Ion Complexes, The Chemical Society, London, 1964.
13 - S. TRIPETT and D.M. WALKER, J. Chem. Soc., 1959, 3874.
14 - G. WITTIG and V. SCHOLLKOPF, Chem. Ber. 1954, **87**, 1318.
15 - E.C. LADD, U.S. Patent 26 32 019, 1953. Chem. Abst. 1954, **48**, 1418.
16 - H.J. BESTMANN, K. ROSTOCK and H. DORNAUER, Angew. Chem. Int. Ed. Engl., 1966, **5**, 308.
17 - D.Y. CURTIN and E.E. HARRIS, J. Am. Chem. Soc., 1951, **73**, 4519.
18 - B. DESCHAMPS, G. LEFEBVRE, A. REDJAL and J. SEYDEN-PENNE, Tetrahedron, 1973, **29**, 2437.
19 - L. HENRY, Chem. Zent., II, 1898, 662.
20 - D.T. MOWRY, J. Am. Chem. Soc., 1945, **67**, 1050.
21 - G. WITTIG and H. HARTMANN, Chem. Ber., 1939, **72**, 1387.
22 - J.N.E. DAY and J.F. THORPE, J. Chem. Soc., 1920, 1473.
23 - P.B. CORSON and R.W. STOUGHTON, J. Am. Chem. Soc., 1928, **50**, 2829.
24 - O. MOLDENHAUER, W. IRION and H.O. MARWITZ, Germ. Pat. 950915, 1956. Chem. Abst. 1959, **53**, 2251.
25 - P.G. GARDNER and R.L. BRANDON, J. Org. Chem., 1957, **22**, 1704.
26 - H. KISCH and O.E. POLANSKY, Tetrahedron Lett. 1969, 805.
27 - C.A. KINGSBURG, D. DRANEY, A. SOPCHIK, W. RISSLER and D. DURHAM, J. Org. Chem., 1976, **41**, 3863.
28 - A.C. COPE and K.E. HOYLE, J. Am. Chem. Soc., 1941, **63**, 733.