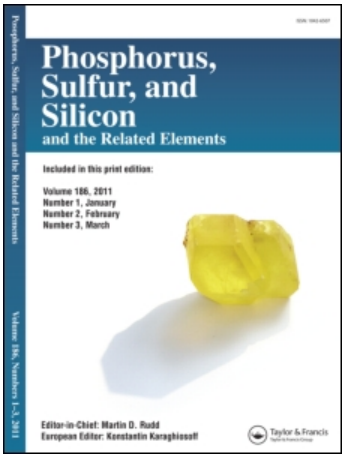

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THE HWE REACTION IN SOLID – LIQUID TWO PHASE SYSTEM FOR THE SYNTHESIS OF α,β-UNSATURATED AMIDES

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The Horner-Wadsworth-Emmons (HWE) reaction of the diethyl ester of 2-amino-2-oxoethylphosphonic acid **1** as well as of diethyl ester of the 2-dimethylamino-2-oxoethylphosphonic acid **2** with some aldehydes and ketones **3** in liquid-solid two phase system is used for the preparation of α,β-unsaturated amides **4, 5**. The synthesis is carried out in mild conditions (room temperature, KOH, K_2CO_3, CaO) in the absence of a catalyst or in the absence of a solvent, and leads in very high (E)-stereoselectivity and in high yields to en-amides.

Keywords: Diethyl ester of 2-amino-2-oxoethylphosphonic acid; diethyl ester of 2-diethylamino-2-oxoethylphosphonic acid; Horner-Wadsworth-Emmons reaction; α,β-unsaturated amides; solid-liquid two phase system

INTRODUCTION

Lately the interest in α,β-unsaturated amides has distinctly increased because of their high physiological activity as anticonvulsant[1] and tranquilisant[2] agents, pesticides[3] etc. Besides the traditional methods for synthesis of amides, namely the reaction of acid's derivatives with ammonia and amines[4], hydrolysis of nitrile[5], the condensation of aldehydes with amines[6], the reaction of Horner-Wadsworth-Emmons(HWE) using phosphine oxide and phosphonate carbanions, is a convenient method for the preparation of unsaturated amides. Their synthesis is described from the

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alkaline derivatives of α-amido-phosphonates, obtained in anhydrous solvents and strong bases, such as NaH, RONa, LDA[7].

The technique of phase-transfer catalysis is widely used in organic synthesis. The HWE reaction for the synthesis of alkenes, unsaturated esters, nitriles and ketones is studied in heterogeneous media (liquid – liquid or solid – liquid)[8-12], in the absence of the typical phase transfer catalysts[13] or in the absence of solvent[14].

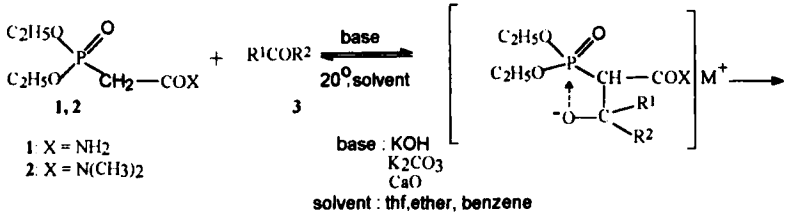
We report herein a convenient way for the preparation of α-β-unsaturated amides using the Horner-Wadsworth-Emmons reaction in a liquid-solid two phase system at room temperature with accessible bases (KOH, K_2CO_3, CaO) and solvents in the absence of a catalyst.

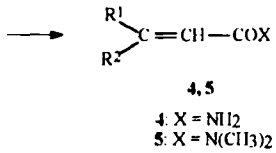
RESULTS AND DISCUSSION

We have studied the reaction of the diethyl ester of 2-amino-2oxoethylphosphonic acid **1** as well of the diethyl ester of 2-dimethylamino-2-oxoethylphosphonic acid **2** with some aldehydes and ketones **3** in the presence (in most cases) of potassium hydroxide in a ratio of the reagents amide/carbonyl compound/KOH 1:1:2 in tetrahydrofurane (thf), diethyl ether or benzene (see experimental part). In the experiments with aldehydes after vigorous stirring for 15–60 min. at room temperature the corresponding α,β-unsaturated amides **4,5** were obtained in high yields, good purity and stereoselectivity.

In order to optimize the reaction, it was carried out under different conditions (solvent, base, reaction time, see Table I). The experiments showed that both polar and nonpolar solvents (thf, diethyl ether and benzene) are suitable media for this liquid-solid two phase reaction. Obviously, the polar media is appropriate for solvating of the carbanions, formed at the interface, while in benzene the second (unreversible) stage of the reaction is shifted to the enamides **4,5** because of their lower solubility in this solvent. The decrease of the reaction time leads to a lowering of the yields of the en-amides.

Potassium hydroxide was the best deprotonating base; its exchange with potassium carbonate decreased the yields. The rate of formation of the carbanion could not be increased even by warming[9] – after heating for 1 hr at 70°C of the reaction mixture containing potassium carbonate the yield of





4, 5

4: X = NH2
5: X = N(CH3)2

3	R1	R2
3a	C_6H_5	H
3b	C_6H_4-Cl-4	H
3c	$C_6H_5CH{=}CH$	H
3d		H
3e		H
3f		
3g	C_6H_5	CH_3

SCHEME 1

succinamide is more than twice lower than in the presence of potassium hydroxide (see Table I).

It is known from the literature that the deprotonation of CH- acids can be realized also in the absence of a base when boiling in ethanol[21]. Our experiment showed that the most reactive of the chosen aldehydes, 4-chloro-benzaldehyde **3b**, when kept for 3 hr. in ethanol at reflux did not react with **1** (the aldehyde was isolated quantitatively as 2,4-dinitrophenyl-hydrazon).

The HWE reaction is found to be successful for cyanomethanephosphonates and methylendiphosphonates with benzaldehyde on solid bases without the use of solvents[14]. Our experiment with **1** and **3a** in the presence of calcium oxide as described in ref.[14] confirmed this possibility, although the yield of the succinamide **4a** was not so high as in the optimized conditions (thf or benzene, KOH) – the yield of the preparatively isolated **4a** was 70%, determined by gas chromatography (GC) – 71%.

TABLE I Yields and reaction conditions for preparaton of enamides **4**and **5**

1,2	*3*	*Solvent*	*Rase*	*Time (min)*	*4, 5*	*Yield of 4, 5*	*Lit.*
1	**3a**	ether	KOH	60	**4a**	92	15
1	**3a**	ether	KOH	15	**4a**	79	
1	**3a**	thf	KOH	60	**4a**	86	
1	**3a**	benzene	KOH	60	**4a**	91	
1	**3a**	–	CaO	1440	**4a**	70[a]	
1	**3a**	thf	K_2CO_3	60[b]	**4a**	38	
1	**3b**	EtOH	–	180	**4b**	0[c]	
1	**3c**	thf	KOH	60	**4c**	82	5
1	**3d**	thf	KOH	60	**4d**	75	16
1	**3e**	thf	KOH	60	**4e**	89	6b
1	**3f**	thf	KOH	60	**4f**	57	17
1	**3f**	ether	KOH	60	**4f**	46	
1	**3f**	benzene	KOH	60	**4f**	40	
1	**3g**	thf	KOH	60[b]	**4g**	30	18
1	**3g**	benzene	KOH	60	**4g**	13	
2	**3a**	thf	KOH	60	**5a**	99	7
2	**3c**	thf	KOH	60	**5c**	88	4a
2	**3d**	thf	KOH	60	**5d**	78	19
2	**3e**	thf	KOH	60	**5e**	85	20

a. by GC.
b. at 70 °C.
c. 99 % of 2,4-dinitrophenylhydrazone of benzaldehyde, m.p. 278–279 °C.

The present results indicate that the reactivity of amide **1a** towards aldehydes in the presence of weak bases is lower than the reactivity of the corresponding ester[11] and nitrile[14], which could be explained with the weaker CH-acidity of the amides [the pK_A values in DMSO of $(EtO)_2P(O)CH_2CONEt_2$, $(EtO)_2P(O)CH_2COOEt$ and $(EtO)_2P(O)CH_2CN$ are respectively 22.6, 19.2 and 17.6][22] thus decreasing the rate of the stade of carbanion formation.

The reaction of the amide **1** and ketones **3f** and **3g** in the for aldehydes optimized conditions (see Experimental) proceeds with moderate yields (46–57%). The reaction rate with **3f** could not be increased by the prolongation of the reaction time – after 24 hr. at room temperature the yield of **4f** does not change and the purity of the product is worse, probably due to a side process. The lower activity in the A_N reactions of the ketones **3f** and **3g** compared to the aldehydes **a-e** probably influences the aldol stage of the reaction. The decrease of yield of the amides **4f** and **5g** could be due to the higher steric hindrance in the ketones, thus provoking a lower energetic barrier of the retroaldol stage of the reaction. Our previous NMR data have shown strain rotation of the phenyl group only of the intermediates with ketones[23].

The HWE reaction at the conditions of two phase system is found to proceed in most cases stereoselectively towards the (E)- isomers[9,12,13]. Rarely the stereoselectivity is lacking, for example with cyanomethanephosphonate and ortho-substituted aldehydes[9], as well as in the "dry" reaction of the same nitrile on calcium oxide[14]. Our studies showed that the reaction of phosphonoamides **1** and **2** with aldehydes is highly (E)-stereoselective, even on calcium oxide. The quantity of the (Z)- isomers, determined by ^1H NMR and GC was less than 5%. Only by the reaction of **1** with acetophenon **3g** a mixture of (E) – and (Z) isomers **4g** was isolated in a ratio (E)/(Z) 76:24 (determined by ^1H NMR) independant on the nature of the solvent (thf, benzene). Similarly, a lack of stereoselectivity of the HWE reaction with **3g** was noticed before[23,24].

The configuration of the **4g** was proved by measuring the ^{13}C NMR spectra with gated decoupling of a mixture of (E) and (Z) – **4g** (95:5). The coupling constants of $^3J_{CH} = 7.8$ Hz for the (E) isomer and $^3J_{CH} = 7.1$ Hz for the (Z) isomer were found for the three bond coupling constant across a double bond. The observed small difference in the $^3J_{CH}$ coupling constants for (E) and (Z) isomers is not unusual – there are literature data for similar compounds with very small difference in their (E)- and (Z)- vicinal coupling constants[25,26]. In conclusion, the above described reaction in two phase system has the advantage to avoid the strong bases and anhydrous solvents. It proceeds in mild conditions in the absence of a catalyst, as well as in the absence of a solvent, with very high stereoselectivity and thus offering a convenient and easy method for the preparation of α,β-unsaturated amides.

EXPERIMENTAL

The phosphonamides **1** and **2** were obtained using literature methods[16,17]. The carbonyl compounds **3** were distilled before use. The ir spectra were recorded on a Specord IR-71 spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker DRX-250 spectrometer at room temperature and referenced to internal TMS. The qualitative TLC investigations were carried out on silicagel $60F_{254}$ (aluminium sheets "Merck") using diethyl ether-ethylacetate 1:1 as mobile phase. For GC analyses a chromatograph with FID detector and OV-17 (Perkin-Elmer) was used.

The HWE reaction in solid-liquid two phase system for the preparation of the amides 4 and 5

A solution of **1** or **2** (5 mmol) and the carbonyl compound **3** (5 mmol) in 18–20 ml of the solvent (thf; diethylether; benzene) was added to a suspension of powdered potassium hydroxide (10 mmol) in 5 ml of the corresponding solvent and the mixture was stirred at room temperature for 15–60 min. The solvent was evaporated in the vacuum and the a crude product was washed by stirring with cold water (3x2 cm^3) to give after drying the corresponding enamide **4** (**5**) with high purity (TLC, ir, m.p.).

The HWE dry reaction of 1 and 3a on calcium oxide

To a solution of 0.980 g (5 mmol) of **1** and 0.530 g (5 mmol) of **3a** in 10 ml of anhydrous methylene chloride, 3.00 g of calcium oxide was added and the solvent was rapidly evaporated under vacuum. The reaction mixture was allowed to stay 24 hr. at room temperature, after that it was extracted with methylene chloride (3x30 cm^3) and the solvent was evaporated in the vacuum. The crude product (**4a**) was washed with cold water (10 cm^3) and dried at 70–80°C. The yield (determined by GC) of **4a** was 70 %.

(E)-**4d**: ^{1}H NMR[27] (DMSO): 6.04(s, 2H, CH_2), 6.43(d, ^{3}J = 15.3 Hz, 1H, CH-CO), 6.92(d, ^{3}J = 8.0 Hz, 1H, m-Ph), 7.00(bs, 1H, syn-NH), 7.03(dd, ^{3}J = 8.0 Hz, ^{4}J = 1.4 Hz, 1H, o-Ph), 7.13(d, ^{3}J = 1.4 Hz, 1H, o-Ph), 7.31(d, ^{3}J = 15.3 Hz, 1H, CH-Ph), 7.41(bs, 1H, anti-NH).

^{13}C NMR (DMSO): 101.5(CH_2), 106.3(o-Ph), 108.7(m-Ph), 120.5(CH-CO), 123.4(o-Ph), 129.4(i-Ph), 139.1(CH-Ph), 148.0(p-Ph), 148.6(m-Ph), 167.0(C=O).

(E)-**4e**: ^1H NMR (DMSO): 3.67(s, 3H, OCH_3), 3.80(s, 6H, OCH_3), 6.56(d, ^3J = 15.8 Hz, 1H, CH-CO), 6.88(s, 2H, o-Ph), 7.06(bs, 1H, syn-NH), 7.35(d, ^3J = 15.3 Hz, 1H, CH-Ph), 7.48(bs, 1H, anti-NH).

^{13}C NMR (DMSO): 56.0(m-OCH_3), 60.2(p-OCH_3), 105.1 (o-Ph), 121.7(CH-CO), 130.6(i-Ph), 138.8(p-Ph), 139.6(CH-Ph), 153.2(m-Ph), 167.0(C=O).

(E)-**4g**: ^1H NMR ($CDCl_3$): 2.56(d, ^4J = 1.2 Hz, 3H, CH_3), 5.61(bs, 2H, NH), 6.07(q, ^4J = 1.2 Hz, 1H, CH), 7.34–7.46(m, 5H, Ph).

^{13}C NMR ($CDCl_3$): 17.6(CH_3), 118.9(CH), 126.1(o-Ph), 128.4(m-Ph), 128.5(p-Ph), 142.4(i-Ph), 152.0(C=), 169.2(C=O).

(Z)-**4g**: ^1H NMR ($CDCl_3$): 2.16(d, ^4J = 1.5 Hz, 3H, CH_3), 5.67(bs, 2H, NH), 5.91(q, ^4J = 1.5 Hz, 1H, CH), 7.34–7.46(m, 5H, Ph).

^{13}C NMR ($CDCl_3$): 27.0(CH_3), 121.9(CH), 125.6(p-Ph), 126.9(o-Ph), 128.8(m-Ph), 139.8(i-Ph), 149.3(C=), 168.9(C=O).

(E)-**5d**: ^1H NMR[28](DMSO): 2.88(s, 3H, syn-NCH_3), 3.11(s, 3H, anti-NCH_3), 6.03(s, 2H, CH_2), 6.89(d, ^3J = 8.0 Hz, 1H, m-Ph), 7.02(d, ^3J = 15.3 Hz, 1H, CH-CO), 7.10(dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1H, o-Ph), 7.35(d, ^3J = 15.3 Hz, 1H, CH-Ph), 7.40(d, ^4J = 1.4 Hz, 1H, o-Ph).

^{13}C NMR (DMSO): 35.5(syn-NCH_3), 37.0(anti-NCH_3), 101.6(CH_2), 106.7(o-Ph), 108.5(m-Ph), 116.6(CH-CO), 124.2(o-Ph), 129.8(i-Ph), 141.1(CH-Ph), 148.1(p-Ph), 148.6(m-Ph), 166.0(C=O).

(E)-**5e**: ^1H NMR (DMSO): 2.93(s, 3H, syn-NCH_3), 3.17(s, 3H, anti-NCH_3), 3.68(s, 3H, OCH_3), 3.82(s, 6H, OCH_3), 7.02(s, 1H, o-Ph), 7.14(d, ^3J = 15.4 Hz, 1H, CH-CO), 7.41(d, ^3J = 15.4 Hz, 1H, CH-Ph).

^{13}C NMR (DMSO): 35.4(syn-NCH_3), 37.0(anti-NCH_3), 56.1(m-OCH_3), 60.2(p-OCH_3), 105.7(o-Ph), 117.8(CH-CO), 130.9(i-Ph), 138.8(p-Ph), 141.4(CH-Ph), 153.1(m-Ph), 165.7(C=O).

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