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Phosphorus, Sulfur, and Silicon and the Related Elements

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Jordanka Petrova^a, Snezhana Momchilova^a & Nikolay G. Vassilev^b

^a Faculty of Chemistry, Sofia University "St. KI. Ochridski", I James Bourchier Avenue, Sofia, 1164, Bulgaria

^b Institute of Organic Chemistry, Bulgarian Academy of Sciences, 1113, Sofia, Bulgaria Published online: 27 Oct 2006.

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

JORDANKA PETROVA^{a*}, SNEZHANA MOMCHILOVA^a and NIKOLAY G. VASSILEV^b

^aFaculty of Chemistry, Sofia University "St. Kl. Ochridski", 1 James Bourchier Avenue, Sofia 1164, Bulgaria and ^bInstitute of Organic Chemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

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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, K₂CO₃, 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 anticonvulsant¹ and tranquilisant² agents, pesticides³ etc. Besides the traditional methods for synthesis of amides, namely the reaction of acid's derivatives with ammonia and amines⁴, hydrolysis of nitrile⁵, the condensation of aldehydes with amines⁶, 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

^{*} Corresponding Author.

alkaline derivatives of α -amido-phosphonates, obtained in anhydrous solvents and strong bases, such as NaH, RONa, LDA⁷.

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 catalysts¹³ or in the absence of solvent¹⁴.

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, K₂CO₃, CaO) and solvents in the absence of a catalyst.

RESULTS AND DISCUSSION

We studied the reaction of diethyl of have the ester 2-amino-20x0ethylphosphonic 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 carbonion could not be increased even by warming⁹ – after heating for 1 hr at 70°C of the reaction mixture containing potassium carbonate the yield of



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 ethanol²¹. 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 solvents¹⁴. 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%.

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

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

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 ester¹¹ and nitrile¹⁴, 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.

ENAMIDES

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 ketones²³.

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 aldehydes⁹, as well as in the "dry" reaction of the same nitrile on calcium oxide¹⁴. 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 ¹³C NMR spectra with gated decoupling of a mixture of (E) and (Z) – **4g** (95:5). The coupling constants of ${}^{3}J_{CH} = 7.8$ Hz for the (E) isomer and ${}^{3}J_{CH} = 7.1$ Hz for the (Z) isomer were found for the three bond coupling constant across a double bond. The observed small difference in the ${}^{3}J_{CH}$ 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 ¹H and ¹³C-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 ($3x2 \text{ cm}^3$) 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 ($3x30 \text{ cm}^3$) and the solvent was evaporated in the vacuum. The crude product (4a) was washed with cold water (10 cm³) and dried at 70–80°C. The yield (determined by GC) of 4a was 70 %.

(E)-4d: ¹H NMR²⁷ (DMSO): 6.04(s, 2H, CH₂), 6.43(d, ³J = 15.3 Hz, 1H, CH-CO), 6.92(d, ³J = 8.0 Hz, 1H, m-Ph), 7.00(bs, 1H, syn-NH), 7.03(dd, ³J = 8.0 Hz, ⁴J = 1.4 Hz, 1H, o-Ph), 7.13(d, ³J = 1.4 Hz, 1H, o-Ph), 7.31(d, ³J = 15.3 Hz, 1H, CH-Ph), 7.41(bs, 1H, anti-NH).

ENAMIDES

¹³C NMR (DMSO): 101.5(CH₂), 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, OCH₃), 3.80(s, 6H, OCH₃), 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).

¹³C NMR (DMSO): 56.0(m-OCH₃), 60.2(p-OCH₃), 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 (CDCl₃): 2.56(d, ⁴J = 1.2 Hz, 3H, CH₃), 5.61(bs, 2H, NH), 6.07(q, ⁴J = 1.2 Hz, 1H, CH), 7.34–7.46(m, 5H, Ph).

¹³C NMR (CDCl₃): 17.6(CH₃), 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 (CDCl₃): 2.16(d, ⁴J = 1.5 Hz, 3H, CH₃), 5.67(bs, 2H, NH), $5.91(q, {}^{4}J = 1.5 Hz, 1H, CH)$, 7.34-7.46(m, 5H, Ph).

¹³C NMR (CDCl₃): 27.0(CH₃), 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 NMR²⁸(DMSO): 2.88(s, 3H, syn-NCH₃), 3.11(s, 3H, anti-NCH₃), 6.03(s, 2H, CH₂), 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).

¹³C NMR (DMSO): 35.5(syn-NCH₃), 37.0(anti-NCH₃), 101.6(CH₂), 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-NCH₃), 3.17(s, 3H, anti-NCH₃), 3.68(s, 3H, OCH₃), 3.82(s, 6H, OCH₃), 7.02(s, 1H, o-Ph), 7.14(d, ${}^{3}J = 15.4$ Hz, 1H, CH-CO), 7.41(d, ${}^{3}J = 15.4$ Hz, 1H, CH-Ph).

¹³C NMR (DMSO): 35.4(syn-NCH₃), 37.0(anti-NCH₃), 56.1(m-OCH₃), 60.2(p-OCH₃), 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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