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A Convenient Synthesis of Enamides and Dienamides by Horner-Wittig and Wadsworth-Emmons Reactions

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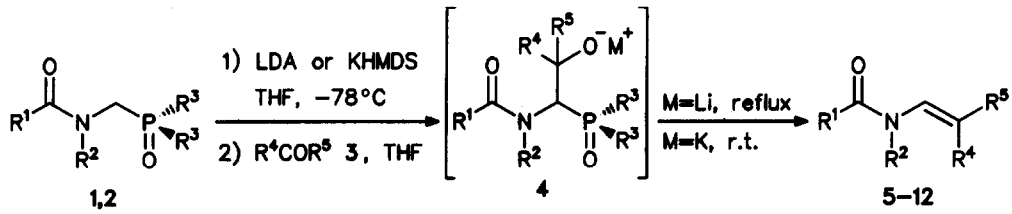
Abstract: *Various N-acyl-N-alkyl-1-amino-alkenes and -1,3-dienes have been efficiently prepared by reacting aldehydes or ketones 3 with N-alkyl-N-(diphenylphosphinoyl)methyl and -N-(diethoxyphosphoryl)methyl carboxamides 1, 2.*

N-acyl-*N*-alkyl-1-amino-alkenes and -1,3-dienes are a class of conjugated compounds of increasing interest in organic synthesis.[1] For instance, the photocyclization of aromatic enamides has been established as one of the most useful cyclization reactions for constructing six-membered lactams[2] and has been remarkably exploited in the area of alkaloid total synthesis.[3] In the last few years, the use of dienamides[4] in both inter- and intramolecular Diels-Alder reactions has been impressively exemplified,[5] especially for the elaboration of natural products.[6] Recent reports from our laboratory showed the utility of (poly)cyclic dienamides for the construction of diversified spirooxazines, thiazines and selenazines.[7]

The main methods for the preparation of these conjugated compounds involve acylation of aldimines[8] and vinylimines[9] with carboxylic acid chlorides in the presence of a tertiary amine or the multistep reaction sequence: anionisation, alkylation and basic elimination from α-carbamidosulfones.[10] A convenient preparation of 1-*N*-acylamino-1,3-dienes from dienoic acids by a modified Curtius procedure has been reported but this route leads exclusively to insaturated carbamates.[11] Very recently, Palomo and coworkers described a new method for the preparation of diversely substituted enamides through fluoride ion mediated Peterson alkenation of *N*-[*C,C*-bis(trimethylsilyl)methyl]amido derivatives.[12]

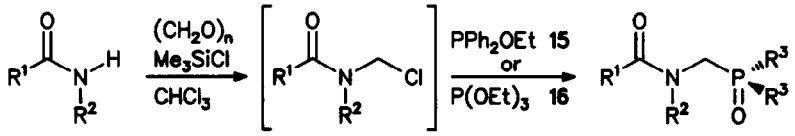
In this paper we report that a variety of *N*-acyl-*N*-alkyl-1-amino-alkenes and -1,3-dienes **5-12** can be efficiently prepared by Horner-Wittig and Wadsworth-Emmons reactions of *N*-(diphenylphosphinoyl)methyl or *N*-(diethoxyphosphoryl)methyl carboxamides, **1**, **2** respectively, with suitable aldehydes and ketones **3** (scheme 1, Table). A rather similar strategy has been successfully utilized to convert aromatic and aliphatic aldehydes into their homologous enamines.[13]

The *N*-alkyl-*N*-(diphenylphosphinoyl)methyl and -*N*-(diethoxyphosphoryl)methyl carboxamides, **1** and **2** were prepared by treatment of the crude chloromethylcarboxamides **14**[14] with ethyl diphenylphosphinite **15**[15] or triethylphosphite **16** (scheme 1).[16] This method proved more convenient than the treatment by chlorodiphenylphos-



scheme 1

phine of *N*-(α-alkoxyalkyl)-amides which can only be prepared by a few limited methods[17] such as anodic oxidation of *N*-alkylamides.[18] Various *N*-(1-diphenylphosphinoyl)alkyl carboxamides have been also synthesized by α-amidoalkylation of chlorodiphenylphosphine but the procedure was limited.[19] *N*-(diethoxyphosphoryl)methyl carboxamides can only be prepared by dehydrogenation with Hg(II)-EDTA of dialkylaminomethylphosphonates[20] or by acylation of arylaminomethylphosphonates.[21]



	R¹	R²	R³	yield% (m.p.°C)		R¹	R²	R³	yield%
1a	Ph	Me	Ph	ref. 15	2a	Ph	Me	OEt	90
1b	2-furyl	Me	Ph	90 (118-119)	2b	2-furyl	Me	OEt	87
1c	benzyl	Me	Ph	ref. 15	2d	-(CH₂)₃-		OEt	88
1d	-(CH₂)₃-		Ph	ref. 15					
1e	Ph	benzyl	Ph	ref. 15					

scheme 2

The phosphorylated amides 1 and 2 were smoothly deprotonated at -78°C with lithium diisopropylamide in THF to give an orange solution of the corresponding anions which were subsequently treated with a variety of aromatic, aliphatic aldehydes and ketones and with α,ß-unsaturated aldehydes 3 (scheme 1). Refluxing the reaction mixture for a short period (0.5 h) was necessary to insure completion of the reaction. Results are compiled in Table where it may be seen that this simple procedure affords *N*-acyl-*N*-alkyl-1-amino-alkenes and -1,3-dienes, **5-12** in good yields.

It is noteworthy that the resulting unsaturated carboxamides obtained from the lithiated Horner-Wittig reagents 1 and aromatic and α,ß-unsaturated aldehydes were exclusively obtained as *E*-or *E,E*-isomers.[22] However a much lower degree of stereoselectivity was observed with aliphatic aldehydes and with the phosphonic acid esters 2. All these results are consistent with previous reported findings.[23] The stereoselectivity was also sensitive to the metal counterion in the adducts 4. Thus the treatment of the phosphorylated carboxamides **1a** and **2a** with potassium bis(trimethylsilyl)amide (KHMDS)[24] at -30°C in THF followed by the addition of *p*-anisaldehyde led, after warming to room temperature and usual work-up, to an approximate 75/25 mixture of *Z-/E*-isomers (as judged by NMR).[25,26]

Table. Enamides 5-10 and Dienamides 11,12 Prepared.

Entry	R^1	R^2	R^4	R^5	m.p. (°C)* *E*-isomer	yield% (*E*/*Z*) from 1	from 2
5a	Ph	Me	Ph	H	101-102	92(100/-)	88(90/10)
5b	2-furyl	Me	Ph	H	56-57	90(100/-)	87(90/10)
5c	benzyl	Me	Ph	H	79-80	78(100/-)	
5d		$-(CH_2)_3-$	Ph	H	117-118	85(100/-)	80(95/5)
6a	Ph	Me	p-MeO-C_6H_4	H	94-95	91(100/-)	87(90/10)
6b	2-furyl	Me	p-MeO-C_6H_4	H	52-53	90(100/-)	85(90/10)
7a	Ph	Me	Me	H		45(50/50)	41(60/40)
8a	Ph	Me	cyclohexyl	H		65(60/40)	55(65/35)
8b	2-furyl	Me	cyclohexyl	H		51(60/40)	
9a	Ph	Me	benzyl	H		40(65/35)	41(65/35)
10a	Ph	Me	Ph	Ph	82-83	92	
10e	Ph	benzyl		$-(CH_2)_5-$	85-86[27]	48	
11a	Ph	Me	CH=CH-Ph	H	126-127	88(*E*,*E*-isomer)	
11b	2-furyl	Me	CH=CH-Ph	H	92-93	85(*E*,*E*-isomer)	
12a	Ph	Me	$CH=C(Me)_2$	H		83(*E*,*E*-isomer)	
12b	2-furyl	Me	$CH=C(Me)_2$	H		80(*E*,*E*-isomer)	

* All new compounds gave satisfactory ^1H NMR, mass and IR spectra.

In summary, the procedure described here provides a convenient, simple and versatile method for the preparation of enamides and dienamides from easily accessible Horner-Wittig and Wadsworth-Emmons reagents.

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16. Typical procedure for the synthesis of **1** and **2**. A mixture of the amides (30 mmol), paraformaldehyde (900 mg) and Me_3SiCl (9.8 g, 90 mmol) in $CHCl_3$ (150 mL) was refluxed for 6 h. The mixture was filtered. The solvent and the slight excess of paraformaldehyde were removed under vacuo (5×10^{-2} Torr). The crude chloromethyl carboxamides were dissolved in toluene and were subsequently treated with ethyl diphenylphosphinite **15** (for **1a-e**) or triethyl phosphite **16** (for **2a,b,d**). The mixture was refluxed for 0.5 h and the solvent removed in vacuo. Compounds **1a-e** were obtained by trituration of crude products with ether, filtration and recrystallization from hexane/toluene. Compounds **2a,b,d** were purified by flash column chromatography on silica using a mixture acetone/hexane (7:3) as eluent.
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22. Selected H NMR spectra (CDCl , 400 MHz): **6a**(*E*) δ 3.35 (s, NCH_3), 3.77 (s, OCH_3), 5.99 (d, *J*= 14.4 Hz, ArCH=), 7.08 (b.s, NCH=), 6.70-7.90 (m, 9Haryl). **6b**(*E*) δ 3.41 (s, NCH_3), 3.81 (s, OCH_3), 6.09 (d, *J*= 14.5 Hz, ArCH=), 6.54 (dd, *J*= 0.8, 3.5 Hz, Hfuran), 7.10 (dd, *J*= 0.8, 3.5 Hz, Hfuran), 7.60 (dd, *J*= 0.8, 1.8 Hz, Hfuran), 7.89 (d, *J*= 14.5 Hz, NCH=), 6.70-8.10 (m, 4Haryl). **11a**(*E,E*) δ 3.31 (s, NCH_3), 5.91 (dd, *J*= 10.4, 13.4 Hz, ArCH=CH), 6.49 (d, *J*= 13.4 Hz, ArCH=), 6.78 (bs, NCH=CH), 7.10-7.65 (m, 9Haryl+NCH=). **11b**(*E,E*) δ 3.39 (s, NCH_3), 5.99 (dd, *J*= 10.5, 13.8 Hz, ArCH=CH), 6.51 (dd, *J*= 1.8, 3.5 Hz, Hfuran), 6.53 (d, *J*= 13.8 Hz, ArCH=), 6.80 (dd, *J*= 10.5, 15.5 Hz, NCH=CH), 7.10 (dd, *J*= 0.8, 3.5 Hz, Hfuran), 7.38 (dd, *J*= 0.8, 1.8 Hz, Hfuran), 7.59 (d, *J*= 15.5 Hz, NCH=), 7.10-7.70 (m, 5Haryl).
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25. The *E*- and *Z*-isomers were separated by flash column chromatography using a mixture AcOEt/hexane (1:1) as eluent. H NMR spectrum of **6a**(*Z*) δ 3.08 (s, NCH_3), 3.78 (s, OCH_3), 5.78 (d, *J*= 8.6 Hz, ArCH=), 6.17 (d, *J*= 8.6 Hz, NCH=), 6.85-7.55 (m, 9Haryl).
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