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Communications

Stereocontrolled Syntheses of Substituted Unsaturated δ-Lactams from 3-Alkenamides

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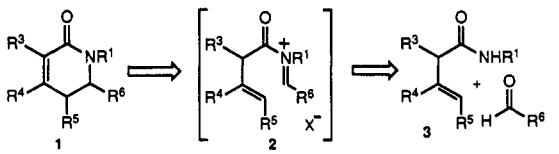
Summary: δ-Lactams have been synthesized with excellent stereocontrol of substituents by condensing 3-alkenamides with aryl aldehydes in polyphosphoric ester.

Efficient stereocontrolled routes to substituted six-membered nitrogen heterocycles are important in view of the array of piperidine,[1] pyridine,[1] quinolizidine,[2] and indolizidine[2,3] alkaloids with pharmacological activity. Syntheses of ipecacuanha alkaloids including emetine have proceeded through intermediary 5,6-dihydro-2(1*H*)-pyridinones.[4] The 5,6-dihydro-2(1*H*)-pyridinone ring system 1[5,6] has considerable potential in synthesis, since it could act as a common intermediate for the synthesis of a wide variety of substituted piperidines, piperidones, pyridines, and pyridones. The versatility of the 5,6-dihydro-2(1*H*)-pyridinone ring system 1 is exemplified by its ability to undergo epoxidation,[5] bromination,[5] and [2 + 2] cycloaddition of the C=C double bond;[7] cuprates effect 1,4-addition,[8] and Michael additions[9] occur with esters.

Scheme I. 5,6-Dihydro-2(1*H*)-pyridinones via [5 + 1] Component Condensations



Remarkably few methods of preparing 5,6-dihydro-2-(1*H*)-pyridinones have been reported;[5,6,10,11] typically, they are nongeneral, require forcing conditions, and do not allow stereocontrolled placement of substituents. We envisaged a convenient route to the pyridinones 1 by a [5 + 1] component condensation of a 3-alkenamide with an aldehyde or ketone (Scheme I). Related processes include the Bischler–Napieralski[12] and Pictet–Spengler reactions[13] and the condensation of 3-alkenamines with formaldehyde equivalents.[14-16]

(1) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1981; Vol. 3, pp 1–90.
(2) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 523.
(3) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1981, Vol. 5, pp 1–54.
(4) Battersby, A. R.; Turner, J. C. *J. Chem. Soc.* **1960**, 717. (b) Fujii, T.; Yoshifugi, S.; Ohba, M. *Chem. Pharm. Bull.* **1978**, *26*, 645.
(5) Kheddis, B.; Bahibah, D.; Hamdi, M.; Perie, J.-J. *Bull. Soc. Chim. Fr.* **1981**, Part 2, 135.
(6) Brandstadter, S. M.; Ojima, I. *Tetrahedron Lett.* **1987**, *28*, 613.
(7) Somekawa, K.; Shimou, T.; Atsuchi, M.; Kumamoto, S. *Nippon Kagaku Kaishi* **1978**, *7*, 1013; *Chem. Abstr.* **1978**, *89*, 128797.
(8) Hagen, T. J. *Synlett* **1990**, 63.
(9) (a) Takano, S.; Sato, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 799. (b) Fujii, T.; Kogen, H.; Yoshifuji; Iga, K. *Chem. Pharm. Bull.* **1979**, *27*, 1847.
(10) (a) Shamma, M.; Rosenstock, P. D. *J. Org. Chem.* **1961**, *26*, 718. (b) Verbiscar, A. J.; Campbell, K. N. *J. Org. Chem.* **1964**, *29*, 2472. (c) Edwards, O. E.; Singh, T. *Can. J. Chem.* **1954**, *32*, 683.
(11) Guareschi, I. *Ann. Chim. Farm.* **1893**, *17*, 83; *Br. Chem. Abstr.* **1893**, 484.
(12) (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74. (b) Kametani, T.; Fukumoto, K. *Chem. Heterocycl. Compd.* **1981**, *38*(1), 139. (c) Belleau, B. *Can. J. Chem.* **1957**, *35*, 651.
(13) (a) Pictet, A.; Spengler, T. *Ber.* **1911**, *44*, 2030. (b) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151. (c) Kametani, T.; Fukumoto, K. In *The Chemistry of Heterocyclic Compounds. Isoquinolines*; Grethe, G., Ed.; John Wiley: New York, 1981; pp 170–182.
(14) (a) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. (b) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (c) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.
(15) Grewe, R.; Hamann, R.; Jacobsen, G.; Nolte, E.; Riecke, K. *Ann.* **1953**, *581*, 85.
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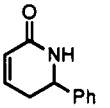
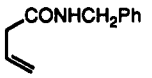
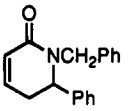
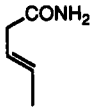
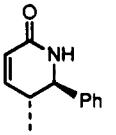
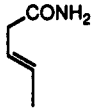
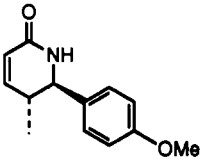
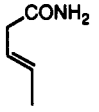
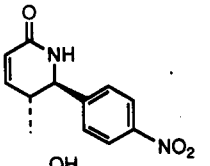
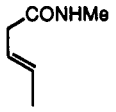
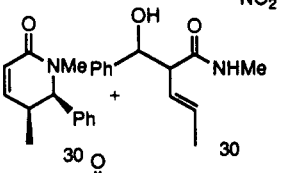
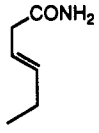
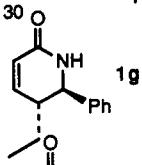
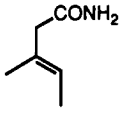
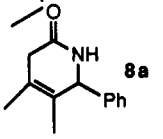
Table I. Synthesis of δ-Lactams from 3-Alkenamides

3-Alkenamide[a]	aldehyde	condns	δ-lactam[b,c]	yield[d] (%)
	PhCHO	PPA 60°C 18h PPE 60°C 16h	**1a** 	30 51
	PhCHO	PPE 60°C 56h	**1b** 	95
	PhCHO	PPE 35°C 24h	**1c** 	63
	*p*-MeO.C$_6$H$_4$.CHO	PPE 45°C 18h	**1d** 	66
	*p*-O$_2$N.C$_6$H$_4$.CHO	PPE 45°C 18h	**1e** 	50
	PhCHO	PPE 40°C 16h	**1f** 	30 30
	PhCHO	PPE 60°C 18h	**1g** 	50
	PhCHO	PPA 40°C 49h PPE 40°C 24h	**8a** 	65 82

[a] (*E*)-3-Pentenamide (85%), mp 70–71 °C, and (*E*)-3-methyl-3-pentenamide (49%), mp 133 °C, were prepared by treatment of the nitriles with alkaline H_2O_2 and tetra-*n*-butylammonium hydrogen sulfate. For related preparations see: Cacchi, S.; Misiti, D.; La Torre, F. *Synthesis* **1980**, 243. Other amides were prepared from the acid chloride and an amine. [b] In a typical reaction, 5 mmol of alkenamide was added to a mixture of 10 mmol of aldehyde in 10 g of PPE or PPA stirred under N_2. [c] All new compounds reported in this paper have been fully characterized by elemental ^{1}H NMR, and ^{13}C NMR analysis (see supplementary material). The relative configuration of lactams was inferred from coupling constants ($J_{vicinal}$ = 11 Hz for the trans-5,6-disubstituted amides **1c** and **1d**, and $J_{vicinal}$ = 3 Hz for the cis-disubstituted amide **1f**). All the depicted configurations refer to racemic materials. [d] Isolated yields. Reaction mixtures were cooled in an ice–salt bath and then 20% aqueous NaOH cautiously added dropwise to give a neutral solution which was extracted with $CHCl_3$.

Condensations under acidic conditions of acyclic β,γ-unsaturated amides with carbonyl compounds to give one or more new rings have only recently been reported,[17] for which a medium of PPA or $MeSO_3H$–P_2O_5 was shown to afford γ-lactams with good stereocontrol. Therefore, in a strategy to obtain 5,6-dihydro-2(1*H*)-pyridinones it would be necessary to exclude such a mode of cationic cyclization in order to realize the alternative ring closure to a δ-lactam. Despite the lack of precedent for such behavior[18] the desired cyclization might proceed a priori through a 6π disrotatory ring-closure[19] in which the amidic carbonyl had undergone enolization or via a cationic cyclization involving an acyliminium species.[20] *We now report the first examples of bond formation between the carbon atom of an aldehyde and the N- and C-4 termini of acyclic 3-alkenamides to give the pyridinone system 1. Table I provides examples of such processes which occur at 30–60 °C, are stereoselective, contiguous stereogenic centers being formed from achiral precursors, and require no Lewis acid*

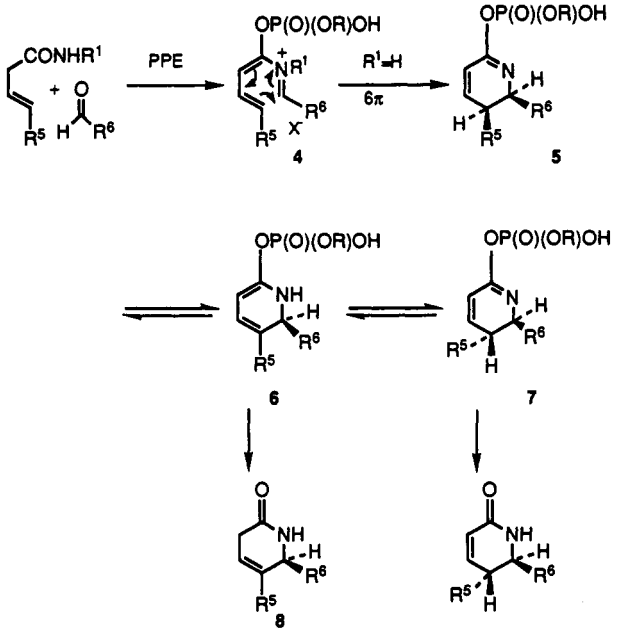
(17) (a) Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1991**, *56*, 2603. For other acid-catalyzed cyclizations to give pyrrolidinones, in which the alkylamide of a bisalkoxycarbonylaminoacetic acid was converted by methanesulfonic acid into a putative cationic intermediate which was trapped by mesylate to give the pyrrolidinone; see: (b) Ben-Ishai, D. *J. Chem. Soc., Chem. Commun.* **1980**, 687. (c) Tamura, Y.; Maeda, H.; Akai, S.; Ishiyama, K.; Ishibashi, H. *Tetrahedron Lett.* **1981**, *22*, 4301.

(18) (a) Belleau, B. *Can. J. Chem.* **1957**, *35*, 663 and 673. For alternative routes to piperidines via *N*-acyliminium species see: (b) Mooiweer, H. H.; Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 3285. (c) Esch, P. M.; Boska, I. M.; Hiemstra, H.; Speckamp, W. N. *Syn. Lett.* **1989**, 38.

(19) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395.

(20) Speckamp, W. N.; Hiemstra, H. *Tetrahedron*, **1985**, *41*, 4367.

Scheme II



catalysts or stabilizing or activating groups.

Condensation of a variety of 3-alkenamides with aldehydes in PPE[21] affords a general route to substituted 5,6-dihydro-2(1*H*)-pyridinones whose stereochemistry can be rationalized by assuming that (*i*) *such cyclizations do not always proceed solely, or at all, through N-acyliminium species; in certain cases, enol phosphate intermediates are involved,* (*ii*) *the formation of a cis-5,6-disubstituted-5,6-dihydro-2(1H)-pyridinone ring is the result of a thermal 6π electrocyclic disrotatory ring-closure,*[22,23] and (*iii*) *trans-5,6-disubstituted-5,6-dihydro-2(1H)-pyridinone rings are formed from the cis-isomers (or their reaction intermediates) by processes which involve a combination of enol phosphate intermediates and equilibration to the trans isomers (as for entries 1c, 1d, 1e, and 1g) either by prototropic shifts or by [1,5]sigmatropic rearrangement of hydrogen.*[23] An uninvestigated possibility is that for amide **1f** (Table I), the 5,6-cis-substituents do not isomerize because the blocking *N*-methyl group precludes the possibility of a [1,5] hydrogen shift. In addition to **1f**, the formation of a β-hydroxy amide (a single diastereoisomer) is consistent with an acid-catalyzed aldol condensation of an enol phosphate intermediate with benzaldehyde. A Prins reaction[18] to account, for example, for the deconjugated amide **8a** cannot be rigorously excluded; however, β-protonation of intermediate **6** appears more plausible.

2,2-Dimethyl-3-pentenamide failed to react with benzaldehyde in PPE at 40 °C, presumably because enolization cannot occur. PPE evidently favors the formation of enol phosphates, and hence δ-lactams via 6π ring closure, unless steric factors prevent coplanarity of the substituents. Thus, condensation of (*E*)-*N*-benzyl-3-pentenamide with benzaldehyde in PPE (35 °C, 24 h) gave exclusively the *N*-benzyl derivative (52%) of the indano-fused γ-lactam previously obtained from a condensation in PPA.[17] A medium of PPA or $MeSO_3H$–P_2O_5 generally favors the formation of the γ-lactam, presumably via *N*-acyliminium cations. However, where this mode would proceed via a primary carbocation, the alternative ring closure operates to give a δ-lactam, e.g, **1a**. Thus, the size of the lactam ring can be controlled exclusively by selection of the acidic medium. In no case studied here was a mixture of γ- and δ-lactams isolated.

In summary, efficient, highly stereocontrolled one-pot syntheses of substituted unsaturated δ-lactams by the condensation of 3-alkenamides with aldehydes in media of phosphoric acids or esters, principally PPE, have been demonstrated. Condensations proceed under mild conditions and can be effected in multigram quantities; activating or stabilizing groups are not required. The reaction medium can critically determine whether a γ-lactam[17] or a δ-lactam is formed. Pathways and synthetic applications are under investigation.

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Registry No. **1a**, 142422-26-2; **1b**, 142422-27-3; **1c**, 142422-28-4; **1d**, 142422-29-5; **1e**, 142422-30-8; **1f**, 142422-31-9; **1g**, 142422-32-0; **8a**, 142422-33-1; PhCHO, 100-52-7; *p*-$MeOC_6H_4CHO$, 123-11-5; *p*-$O_2NC_6H_4CHO$, 555-16-8; $H_2C{=}CHCH_2CONH_2$, 28446-58-4; $H_2C{=}CHCH_2CONHCH_2Ph$, 85390-58-5; (*E*)-$H_3CCH{=}CHCH_2CONH_2$, 133099-99-7; (*E*)-$H_3CCH{=}CHCH_2CONHMe$, 142422-34-2; (*E*)-$H_3CCH_2CH{=}CHCH_2CONH_2$, 133128-00-4; (*E*)-$H_3CCH{=}C(CH_3)CH_2CONH_2$, 142422-35-3.

Supplementary Material Available: Procedures and characterization data for **1a–g** and **8a** (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) PPA was purchased from BDH Chemicals Ltd., Poole. For a review on PPA see: Rowlands, D. A. In *Synthetic Methods*; Pizey, J. S., Ed.; Wiley: New York, 1985; Vol. 6. p 156. For some uses of PPE in synthesis, see: (a) Kanaoaka, Y.; Ban, Y.; Mayashita, K.; Iria, K.; Yonemitsu, O. *Chem. Pharm. Bull.* **1966**, *14*, 934. (b) Kanaoka, Y.; Sato, E.; Yonemitsu, O.; Ban, Y. *Tetrahedron Lett.* **1964**, *35*, 2419. PPE was prepared as described by Cava, M. P.; Lakshmikantham; Mitchell, M. J. *J. Org. Chem.* **1969**, *34*, 2665.

(22) An (*E*)-configuration about the C=N bond has also been assumed. The thermal ring closure might also proceed through an intermediate containing an uncharged nitrogen atom in the case of R^1 = H in Scheme II. The precise constitution of enol phosphate intermediates is not currently known.

(23) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970, pp 114–140. (b) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. (c) Mironov, V. A.; Fedorovich, A. D.; Akhrem, A. A. *Russ. Chem. Rev.* **1981**, *50*, 666.

Synthesis of 1,4-Diketones by Palladium-Catalyzed Reductive Coupling of Acid Chlorides with (*E*)-1,2-Bis(tri-*n*-butylstannyl)ethene or β-Stannyl Enones

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Summary: The palladium-catalyzed coupling of acid chlorides with (*E*)-1,2-bis(tri-*n*-butylstannyl)ethene or β-stannyl enones gives butane-1,4-diones directly by reduction of the intermediate enedicarbonyl derivative by

