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Communications

Stereoselective Syntheses of Substituted γ-Lactams from 3-Alkenamides

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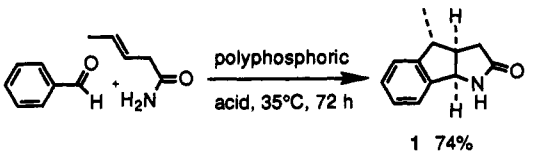
Summary: γ-Lactams and δ-lactams have been synthesized stereoselectively by condensing 3-alkenamides with benzaldehyde in acidic media.

Condensations under acidic conditions of acyclic β,γ-unsaturated amides with carbonyl compounds to give one or more new rings have not been hitherto reported. This is surprising in view of related processes, e.g., (i) the acid-catalyzed cyclodehydration of β-phenethylamides (Bischler–Napieralski reaction[1]), (ii) the condensation of β-arylethylamines with carbonyl compounds (Pictet–Spengler reaction[2]), and (iii) the condensation of 3-alkenamines (with[3] or without[4] silicon termini) with formaldehyde equivalents.

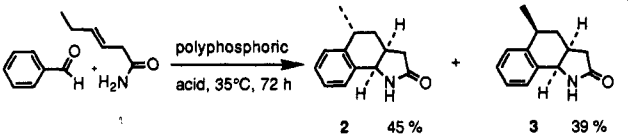
We report here the first examples of bond formation between the carbon atom of an aldehyde and the N and C-3 termini of 3-alkenamides. The processes occur at ~35 °C, are stereoselective, three contiguous stereogenic centers being formed in one pot from achiral precursors, and require no Lewis acid catalysts or stabilizing or activating groups.

Scheme I



1 74%

Scheme II



2 45% 3 39%

Condensation of (*E*)-3-pentenamide[5] (10 mmol) and benzaldehyde (20 mmol) was effected in polyphosphoric acid (PPA;[6] 10 g) at 35 °C for 72 h. After customary workup,[7] column chromatography (silica gel; 40–60 °C 2:1 petroleum ether–ethyl acetate) afforded the tricyclic lactam 1,[8] mp 175–176 °C, from ethyl acetate in 74% yield (Scheme I).

(1) (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74. (b) Kametani, T.; Fukumoto, K. *Chem. Heterocycl. Compd.* **1981**, *38*(1), 139.

(2) (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.

(3) (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.

(4) (a) Grewe, R.; Hamann, R.; Jacobsen, G.; Nolte, E.; Riecke, K. *Ann.* **1953**, *581*, 85. (b) Grob, C. A.; Wohl, R. A. *Helv. Chim. Acta* **1966**, *49*, 2175.

(5) (*E*)-3-Pentenamide, mp 70–71 °C, was prepared in 85% yield by treatment of (*E*)-pentenenitrile 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.

(6) PPA was purchased from BDH Chemicals Ltd., Poole.

(7) Reaction mixtures were poured onto crushed ice, stirred for 20 min, and made alkaline with solid Na_2CO_3, and the suspension was extracted with $CHCl_3$.

(8) All new compounds reported in this paper have been fully characterized by elemental, ^1H NMR, and ^{13}C NMR analysis. The constitution and relative configuration of lactams **1**, **2**, **8**, and **9** were established by single-crystal X-ray analysis. All the depicted configurations refer to racemic materials.

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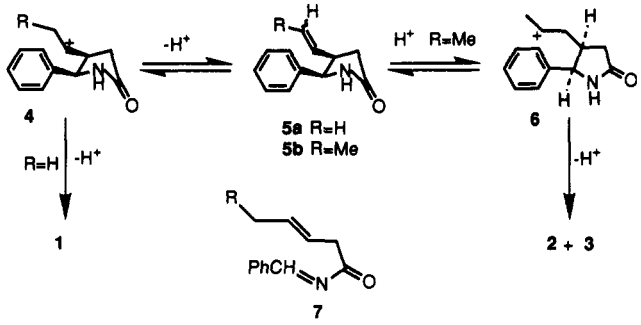
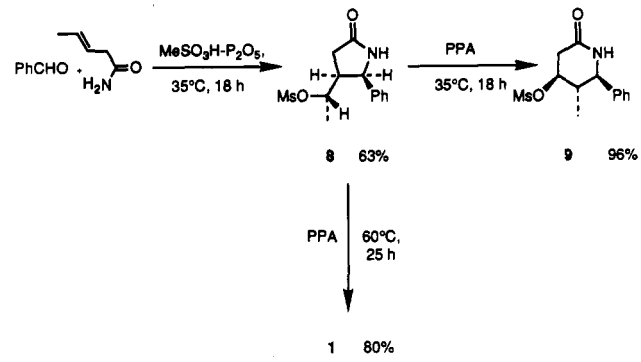
Scheme III



Scheme IV



The formation of a single diastereoisomer of the constitution 1 is notable and was established by single-crystal X-ray analysis. In view of conversions of nitriles into amides by PPA[9] and of many α-amidoalkylations that proceed with use of either nitriles or amides,[10] (*E*)-3-pentenenitrile was substituted for (*E*)-3-pentenamide, whereupon lactam 1 was obtained in 67% yield.

The constitution of 1 and the conversion of 8 into 1 under acidic conditions (vide infra) strongly suggest that the latter part of the overall process involves an intramolecular Friedel–Crafts alkylation.[11] Accordingly, (*E*)-3-hexenamide was examined in an attempt to obtain products unlike 1, but whose formations are consistent with carbocationic mechanisms.

Reaction of (*E*)-3-hexenamide (18 mmol) with benzaldehyde (35 mmol) in PPA (20 g) at 35 °C for 72 h afforded a mixture of isomeric lactams (Scheme II), one of which, 2 (mp 174–176 °C), was isolated in 45% yield by recrystallizing from benzene the crude reaction mixture obtained from the usual workup.[7] The relative configuration of the methyl group was established by single-crystal X-ray analysis.[8] The other lactam, assigned as the epimer 3 on the basis of ^{1}H and ^{13}C NMR data, was obtained in 39% yield.

The high yield of two lactams differing only by *epimeric methyl* groups can be rationalized by the unified pathway of Scheme III; product formation would be controlled by the relative stability of secondary over primary carbocations (for 1), and by the greater thermodynamic stability of lactams 2 and 3 containing central six-membered (as opposed to five-membered) rings. However, the formation of cation 6 via a hydride shift cannot be excluded.

The reaction was probed by using $MeSO_3H$–P_2O_5 (10:1), a medium that has been used as an alternative to PPA.[12] The pyrrolidinone 8,[8,13] mp 159 °C, was isolated in 63%, none of 1 being detected. Pyrrolidinone 8 underwent clean conversion into the isomeric piperidinone 9,[8] mp 162–163 °C, in PPA at 35 °C in 98% yield (Scheme IV). Perhaps surprisingly, no monocyclic pyrrolidinone was isolated when (*E*)-3-hexenamide and benzaldehyde were condensed in $MeSO_3H$–P_2O_5; 2 and 3 (7:6) were formed in 60% yield. Mesylate 8 was converted into the lactam 1 in 80% yield by heating in PPA at 60 °C for 25 h. In a separate experiment (PPA, 35 °C), after 18 h only a small quantity of unreacted 8 and the lactam 1 could be identified. Moreover, since piperidinone 9 was not converted into 1 by PPA at 60 °C for 72 h, but was recovered quantitatively, piperidinone 9 is unlikely to be an intermediate in the formation of 1 from 8. The formation of 9 at 35 °C but not at 60 °C requires further investigation.

The present evidence strongly suggests there are species common to the pathways that lead to the pyrrolidinones[13] *and* to the tricyclic lactams. The present evidence does not permit unequivocal inferences regarding the following: (i) whether acyl imines 7 or their protonated forms are intermediates, (ii) whether other cationic processes[14] are operating, or (iii) whether an imino ene reaction[15] is involved. Formation of the lactams 1–3 could proceed via the *cis*-4,5-disubstituted pyrrolidinones 5 that are topologically related to the acylimines 7 by the *formalism* of an imino ene process.[15] The lack of formation of a monocyclic pyrrolidinone from (*E*)-3-hexenamide may indicate the importance of **5b** and its protonation to give 6. The resulting lactams 2 and 3 containing one five-membered ring may be more readily formed than the tricyclic lactam (which would be formed from 4, R = Me) containing two five-membered rings, analogous to 1, and associated with greater strain and nonbonding interactions than those present in lactams 2 and 3.

The origins of the high diastereoselectivities leading to 8 and 9 can be tentatively interpreted in terms of a cationic alkene cyclization involving a two-electron three-center bonded π-complex[16] for which only the product arising by trans addition across the 3,4-double bond of the 3-alkenamide would be expected owing to the inhibition of rotation about the C=C double bond.[16] Pyrrolidinone 8 would

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(10) The synthesis of a piperidin-2-one that lacks ring fusion by an intramolecular α-amidoalkylation involving an amide or nitrile has not been previously reported. For reviews on α-amidoalkylation, see: (a) Zaugg, H. E. *Synthesis* **1984**, 181. (b) Zaugg, H. E. *Synthesis* **1970**, 49.

(11) Barclay, L. R. C. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley: New York, 1964; Vol. 2, p 785.

(12) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

(13) For other acid-catalyzed cyclizations to give pyrrolidinones, see: (a) Ben-Ishai, D. *J. Chem. Soc., Chem. Commun.* **1980**, 687. The alkylamide of a bis(alkoxycarbonyl)aminoacetic acid was converted by methanesulfonic acid into a putative cationic intermediate that was trapped by mesylate to give the pyrrolidinone. (b) Tamura, Y.; Maeda, H.; Akai, S.; Ishiyama, K.; Ishibashi, H. *Tetrahedron Lett.* **1981**, *22*, 4301.

(14) (a) For 5-*exo*-*trig* cyclizations proceeding with stereocontrol at three contiguous stereogenic centers and believed to proceed by a synchronous transcoplanar attack of an acyliminium ion and formic acid on a double bond, see: Schoemaker, H. E.; Kruk, C.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, *26*, 2437. For Lewis acid induced π-cyclizations affording substituted 3-vinylprolines, see: (b) Mooiweer, H. H.; Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 3285. (c) For an extraordinary tetracyclization involving stereoselective π-cyclization onto an iminium ion in the synthesis of methyl homosecodaphniphyllate, see: Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734.

(15) Several processes considered to be imino ene reactions involve high temperatures; see: (a) Koch, K.; Lin, J.-M.; Fowler, F. W. *Tetrahedron Lett.* **1983**, *24*, 1581. (b) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (c) Lin, J.-M.; Koch, K.; Fowler, F. W. *J. Org. Chem.* **1986**, *51*, 167. However, such reactions have been effected at ~0 °C by using Lewis acids or *N*-tosylimines; see, respectively: (d) Achmatowicz, O.; Pietraszkiewicz, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2680. (e) Melnick, M.; Freyer, A. J.; Weinreb, S. M. *Tetrahedron Lett.* **1988**, *29*, 3891.

(16) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744.

then be converted by PPA into **9**, presumably via the cationic π-complex formed by ring opening. However, a concerted migration of the C-4, C-5 σ-bond and the C–OMs bond in a dyotropic rearrangement[17] would also be predicted to give **9**.

In summary, one-pot stereocontrolled routes to substituted lactams by the condensation of 3-alkenamides with benzaldehyde in acidic media have been demonstrated. Condensations proceed under mild conditions and can be effected in multigram quantities; activating or stabilizing groups are not required. The scope, limitations, pathways, and synthetic applications of these processes are under investigation.

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Supplementary Material Available: IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data for compounds **1**, **2**, **8**, and **9** (4 pages). Ordering information is given on any current masthead page.

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Regioselective Synthesis of Alkylpyrazines

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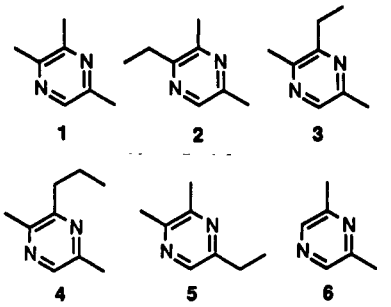
Summary: A new, regioselective synthesis of alkylpyrazines begins with condensation of α-oximido carbonyl compounds with allylamines. The resulting imines are isomerized in the presence of potassium *tert*-butoxide to the corresponding 1-hydroxy-1,4-diazahexatrienes. Thermal electrocyclization–aromatization to pyrazines is best performed after O-acylation of the oximes with methyl chloroformate.

In the last two decades, a large number of alkyl- and cycloalkylpyrazines have been identified mostly as flavor components in food and as alarm pheromones in various species of ants. Owing to their potent and unique organoleptic properties, pyrazines have become greatly appreciated as flavoring materials.[1]

Alkylpyrazines are produced chiefly by self-condensation of α-amino carbonyl compounds and the combination of α-diketones with vicinal diamines followed by dehydrogenation.[2] These methods disappoint in the preparation of unsymmetrically substituted pyrazines because they afford mixtures of regioisomers. The addition of alkyllithium reagents to alkylpyrazines has been utilized for the preparation of some dissymmetrical pyrazines, but the purification of products was often found to be laborious due to incomplete conversion, and, again the formation of isomers.[3a-f]

We describe a new synthesis of alkylpyrazines whose regioselectivity rests on the electrocyclization of 1-hydroxy-1-4-diazahexatrienes. The electrocyclization of *cis,cis*-dienone oximes was studied by Schiess,[4] who found that both rate of formation and yield of substituted *pyridines* could be improved by performing the electrocyclization–aromatization with oxime *O*-benzoates. It seemed reasonable that this concept could be applied to the synthesis of pyrazines by replacing a second carbon atom with nitrogen in the hexatriene precursor, and we have synthesized the six pyrazines (**1**–**6**) using a scheme that is based on this principle.

The oximino ketones **8a–d** (Scheme I) were prepared by condensation of the ketones **7a–d** with isoamyl nitrite in ether containing some hydrochloric acid.[5a-f] Ultraviolet



measurements in neutral and basic solution,[5e] as well as ^{13}C NMR data,[6] revealed anticonfiguration in all oximino ketones thus prepared. Transformation of the ketones **8a–d** to the imines **9a–d** was accomplished by condensation with allylamine in refluxing hexane over molecular sieves (3A).[7] ^{13}C NMR measurements at room temperature established the presence of a single isomer or rapidly interconverting syn and anti forms.[8] A variety of bases caused isomerization of the *N*-allyl imines **9a–d** to the corresponding 2-aza-1,3-butadienes **10a–d**, but we now use mostly a catalytic amount of potassium *tert*-butoxide in DMSO at 50 °C. Under these conditions, the isomerization

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(7) Roelofsen, D. P.; Van Bekkum, H. *Rec. Trav. Chim. Pays-Bas*, **1972**, *91*, 605 and references cited therein.

(8) Tennant, G. *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, p 396.

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