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.

Acknowledgment. We thank the Science and Engineering Research Council and SmithKline Beecham for a CASE award (to U.G.).

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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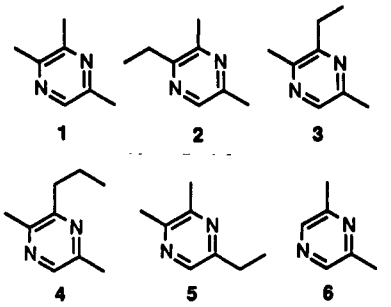
Summary: A new, regioselective synthesis of alkylpyrazines begins with condensation of α-oximido carbonyl compounds with allylamines. The resulting imines are isomerized in the presence of potassium *tert*-butoxide to the corresponding 1-hydroxy-1,4-diazahexatrienes. Thermal electrocyclization–aromatization 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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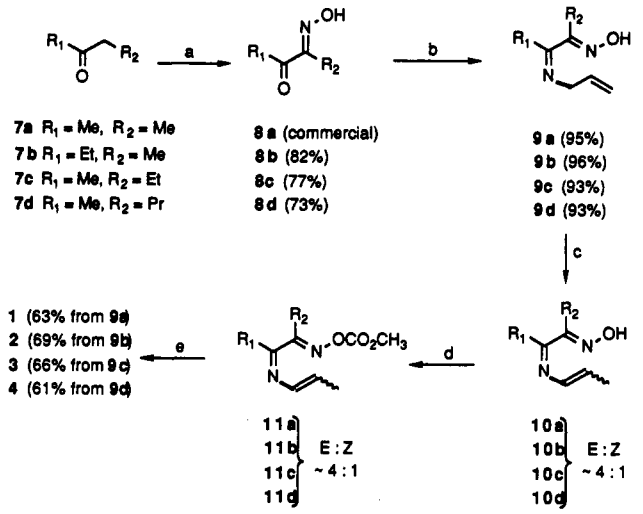
Scheme I[a]



[a] Reaction conditions: a, isoamyl nitrite (0.9 equiv), concd HCl, ether, 10–20 °C, 2 h; b, allylamine (2 equiv), hexane, reflux; c, potassium *tert*-butoxide (0.05 equiv), DMSO, 50 °C, 1–2 h; d, $ClCOOCH_3$ (1.1 equiv), Et_3N (1.2 equiv), CH_2Cl_2, 10–20 °C; e, short contact time pyrolysis in toluene solution at ~300 °C. Due to their instability, compounds **10a–d** and **11a–d** were used in crude form. Intermediates (*E*)- and (*Z*)-**10a**, (*E*)-**10b**, (*E*)-**10c**, (*E*)-**10d**, (*E*)- and (*Z*)-**11a**, (*E*)-**11b**, (*E*)-**11c**, and (*E*)-**11d** could be purified by crystallization from hexane.

yields a mixture of *E* and *Z* isomers, differing in the configuration of the carbon–carbon double bond, in a ratio of approximately 4:1. The individual stereoisomers **10a–d** were stable under these conditions, which means that only the *N*-allyl imines **9a–d** but not the enimines **10a–d** are deprotonated. When the experiments were done in the presence of 1.2 equiv of potassium *tert*-butoxide, the *E* to *Z* ratio changed to 1:2, presumably as a result of kinetically controlled protonation of the anions in the workup. This behavior parallels that of tertiary allyl*amines*.[9] Incidentally, the enimines **10a–d**, not surprisingly, were found to be sensitive to both air and water. Consequently, they are best used for further transformation as mixtures of *E* and *Z* isomers.

In the early stages of this investigation, the electrocyclization–aromatization of a few *O*-methyl derivatives of the diastereomeric enimines **10** were examined. Thermal treatment in boiling xylene or cyclohexanol led to the formation of the anticipated pyrazines but in low yields. Thermolysis of stereochemically pure samples of *Z*-emimines contrary to that of the *E* isomers was slow and inefficient, suggesting that electrocyclization may demand prior conversion to the E isomer. The contrast between *E* and *Z* isomers parallels the behavior of *trans*-2,*cis*-4,-*trans*-6-octatriene, which undergoes electrocyclization 100 times faster than *cis*-2,*cis*-4,*trans*-6-octatriene.[10]

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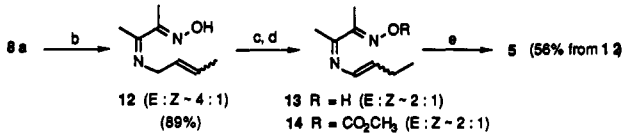
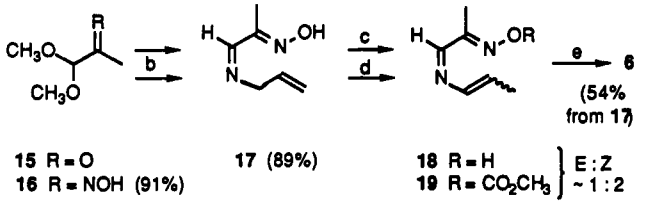
Scheme II



Scheme III



In the course of efforts to improve yields in the final step of this new pyrazine synthesis, we examined the pyrolysis of carbonates **11a–d** prepared by acylation of the oximes **10a–d**.[11] Passage of the carbonates **11a–d** in toluene solution through a glass-lined oven kept at approximately 300 °C afforded the pyrazines. The yields obtained demonstrate that both *E* and *Z* isomers function as pyrazine precursors at this temperature.

Two imines resulting from the condensation of the oximino ketone **8a** with crotylamine[12] and 1-amino-3-butene were briefly evaluated as precursors of pyrazines (Scheme II). Attempted isomerization of the latter failed, meaning that only *allylic* imines serve as intermediates in this pyrazine synthesis. Isomerization of **12** to enimines **13** required 1.3 equiv of potassium *tert*-butoxide in DMSO at 25 °C but acylation to **14** and conversion to pyrazine **5** proceeded as described previously.

For the synthesis of 2,6-dimethylpyrazine (**6**; Scheme III), commercial pyruvaldehyde dimethyl acetal (**15**) was converted to the oxime **16**.[13] Hydrolysis to the unstable aldehyde[14] and condensation with allylamine afforded imine **17**. Sequential isomerization to **18** (1.2 equiv of potassium *tert*-butoxide, THF, 40 °C) and acylation gave carbonate **19**, which was converted to 2,6-dimethylpyrazine (**6**) by thermolysis.

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Supplementary Material Available: Characterization of intermediates and final products (5 pages). Ordering information is given on any current masthead page.

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