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Lactam Synthesis by Intramolecular Ene Insertion of Acylazocarboxylates

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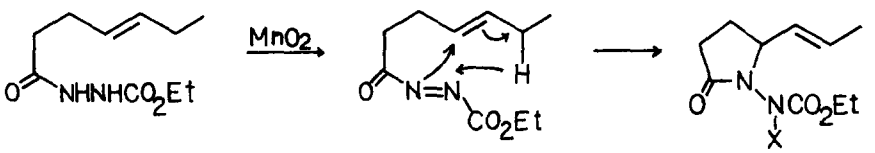
Abstract: Acylazocarboxylates having γ,δ or δ,ε unsaturation are generated by MnO_2 oxidation of the corresponding hydrazines. Internal ene reaction occurs at room temperature to give 5- or 6-membered lactam derivatives.

A recent report by Keck and Webb describes a method for lactam synthesis by intramolecular ene insertion of acylnitroso compounds.[1] We have been working along similar lines to develop routes to α-alkenyl pyrrolidones and piperidones in connection with our interest in ring expansion methods.[2] The key reaction involves intramolecular ene insertion of acylazocarboxylate intermediates.[3,4]

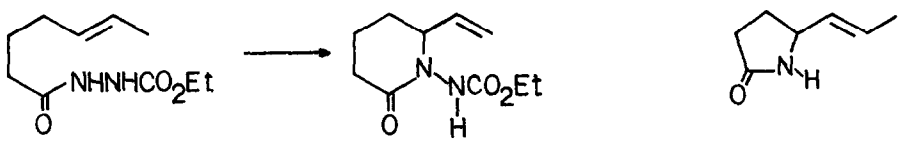
Starting materials 1 and 2 are easily prepared from the γ,δ- or δ,ε-unsaturated acid chlorides and carboethoxyhydrazine. Upon treatment with oxidizing agents which are capable of converting hydrazides into azo compounds, 1 and 2 afford the corresponding ene insertion products 4 (>95% trans olefin) and 5.

Among several oxidizing agents examined, active MnO_2[5,6] at 20°C gave the best results. The hydrazide 1 was stirred mechanically with 25-30 mole excess of MnO_2 in CH_2Cl_2 (20°C bath), resulting in a 67% yield of crystalline 4. The intermediate azo compound 3 did not accumulate

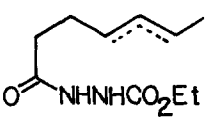
under these conditions, but the characteristic orange color attributed to 3 was observed using other oxidants at lower temperatures. Thus, treatment of 1 with n-C_4H_9Li followed by N-bromosuccinimide at 0°C (THF) gave a transient orange color which faded after a few minutes. However, only 21% of 4 could be isolated from this experiment. Similar results were obtained using lead tetraacetate (38% of 4, CH_2Cl_2, 0°C).



1 3 4 X=H 6 X=CH_3



2 5 7



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Conversion of the ene insertion product 4 into the parent lactam 7 was accomplished by a simple 2-step reduction sequence. Reaction of 4 with KOtBu (1 eq., THF, 0°C) followed by CH_3I (3 eq.) gave an intermediate N-methyl derivative 6 in nearly quantitative yield. Reduction of 6 with Li/NH_3 (-33°C, 3 eq. Li, 0.25 hrs) afforded the lactam 7 (90% overall). Attempted Li/NH_3 reduction of the unmethylated lactam 4 was much slower due to initial formation of the N-lithio derivative, and gave a mixture of 7 (31%) and the acyclic hydrazide 8 (20%) resulting from C–N bond cleavage.

The overall yield of cyclic lactams from starting acyclic carboxylic acids is 40-50%. Keck's acylnitroso method for lactam synthesis gives similar overall yields based on the nitrosocarbonylmethane-9,10-dimethylanthracene 2 + 4 cycloadduct as the starting material.[1] The acylnitroso procedure affords a cleaner ene reaction product and appears better suited for synthesis of structures having added functionality in the lactam ring. On the other hand, the acylazocarboxylates described here are more easily accessible. Both methods employ efficient 2-step reductive sequences to convert the initial ene products into the parent lactams.

Acknowledgement

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References

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6. The yields of ene insertion products appear somewhat dependent on the batch of active MnO_2, especially in the conversion of 2 into 5. Optimum results in this case were obtained by pretreating the active MnO_2 with bis(trimethylsilyl)acetamide (ca. 0.6 m/m of MnO_2 in CH_2Cl_2,

stirred 2 hrs at room temperature after the initial exothermic reaction, filtered, washed with CH_2Cl_2). The MnO_2 so obtained was less reactive (24 hrs to complete oxidation vs. 4-6 hrs without silylation), but the crude product was nearly pure 5, 60-80% mass recovery.

7. Characterization of ene products:

4: (mp 78-80°C from ether), NMR($CDCl_3$, δ): 7.56 (1H, s), 5.84 (1H, dq, J = 16, 6 Hz), 5.36 (1H, dd, J = 16, 8 Hz), 4.20 (3H, m), 2.52-1.60 (4H, m), 1.72 (3H, d, J = 6 Hz), 1.28 (3H, t, J = 8 Hz).

5: (oil), NMR($CDCl_3$, δ): 7.02 (1H, s), 5.84 (1H, m), 5.20 (2H, m), 4.2 (2H, q, J = 7 Hz), 4.4-4.08 (1H, m), 2.52 (2H, t, J = 6 Hz), 2.4-1.6 (4H, m), 1.28 (3H, t, J = 7 Hz).

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