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Pyrolysis of perhydro[1,2-*c*][1,3]oxazines: a green method of synthesizing 2,3-dehydropiperidine enamines

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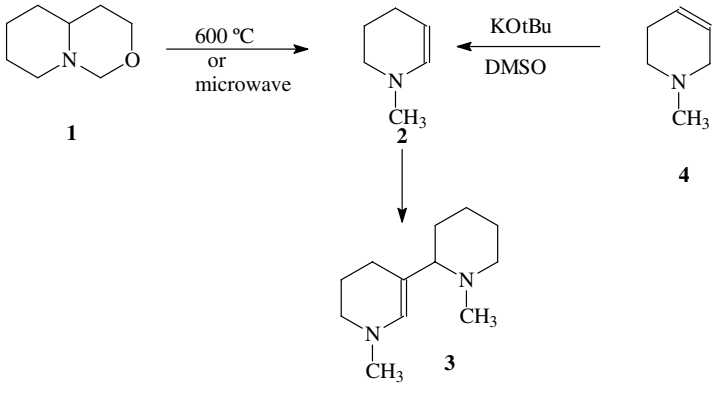
Abstract—Heat pyrolysis of the oxazines formed from 2-piperidineethanol produced 2,3-dehydropiperidine enamines. The same results were observed when these oxazines were irradiated with microwaves. Various 2-substituted perhydrooxazines were synthesized by allowing 2-piperidineethanol or 2-piperidinemethanol to react with aldehydes or ketones.

The synthesis of 2,3-dehydropiperidine enamines[1] has typically been carried out by one of the following methods: oxidation of saturated piperidines with mercuric acetate,[2] reduction of aromatic heterocycles[3] and amides,[4] addition of Grignard reagents to lactams,[5] and base catalyzed isomerizations of 1,2,5,6-tetrahydropyridines.[6,7]

We have found that perhydro[1,2-*c*][1,3]oxazines are a good source of various *N*-substituted 2,3-dehydropiperidine enamines. These enamines can be produced using only the 'green' reactions of flash vacuum thermolysis or microwave excitation of these oxazines. The thermolysis temperatures used were 600–750 °C. For example, when 3-oxa-1-azabicyclo[4.4.0]decane[8] (**1**) was passed through a pyrolysis apparatus,[9] enamine **2** was produced in a 43% yield (Scheme 1). Upon standing this enamine reacted to form dimer **3**.[2] These products were shown to have identical physical and spectral properties (IR, NMR and MS) as those obtained by base isomerization of compound **4**[6] (see Table 1). A similar result was obtained by the use of microwave energy in a microwave apparatus.[10]

In a parallel reaction, 2-phenyl-3-oxa-1-azabicyclo-[4.4.0]decane[11] (**5**) was pyrolyzed to produce enamine



Scheme 1.

Keywords: Oxazines; Pyrolysis; Microwave; Enamines; Azomethine ylides.
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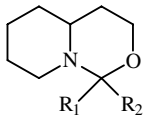
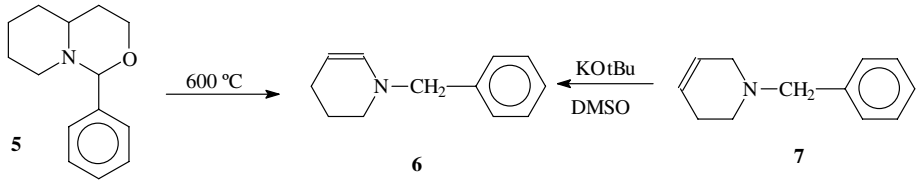
Table 1. Yields, physical and spectral properties of bicyclo[4.4.0]decyl oxazines and enamines



R_1	R_2	Oxazine % yield	Boiling point °C (mmHg)	Enamine % yield					Enamine mass spectra	IR (cm^{-1})[b] N–C=C	
				Pyrolysis	Microwave	GC/MS[a]				Monomer	Dimer
						120	240	290			
H[c]	H	80	85–87 (0.6)	43	38	0	14	20	97(M^+)	1645	1670
CH_3[c]	H	77	60–65 (1.5)	—	—	0	6	11	111(M^+) 96(base)	—	—
Ph[d]	H	97	55–56[e]	6	—	0	4	20	173(M^+) 91(base)	1642	—
p-MePh[f]	H	55	64–65[e]	—	—	0	6	8	187(M^+) 105(base)	1640	—
p-ClPh[g]	H	70	69–70[e]	5	24	2	5	6	207(M^+) 125(base)	1643	—
p-HOPh[f]	H	79	156.5–157.5[e]	—	—	0	0	5	189(M^+) 55(base)	—	—
p-MeOPh[f]	H	80	64–65[e]	13	—	0	19	58	203(M^+) 121(base)	1646	1673
m-MeOPh[f]	H	68	82 (0.6)	—	—	0	8	17	203(M^+) 121(base)	—	—
p-O_2NPh[g]	H	95	93–94[e]	—	—	0	3	3	218(M^+) 55(base)	—	—
m-O_2NPh[f]	H	94	164–166 (0.2)	—	—	0	1	5	218(M^+) 55(base)	—	—
Cyclohexyl[h]		87	85–95 (0.5)	20	—	1	44	63	165(M^+) 122(base)	1644	1668
Cyclopentyl[h]		86	71–73 (0.1)	13	—	3	36	52	151(M^+) 122(base)	1646	1673
Bicyclo[2.2.1]heptyl[f]		60	89–92 (0.2)	17	—	16	63	78	177(M^+) 96(base)	1642	1683

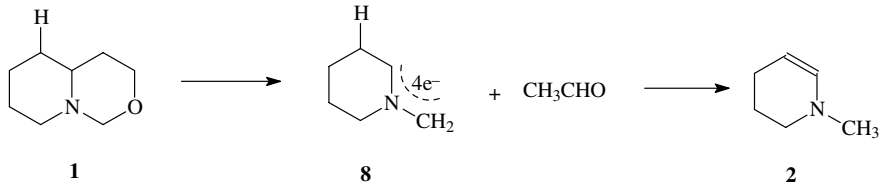
[a] A Phenomenex Zebron ZB-5 30-meter column in a Hewlett Packard BCD Plus GC–MS system was used.
[b] Obtained as a liquid film using a Thermo Nicolet Nexus 670 FT-IR spectrophotometer.
[c] Ref. 8.
[d] Ref. 11.
[e] Melting point.
[f] Satisfactory elemental analysis was obtained. Performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.
[g] Ref. 20.
[h] Ref. 15.



Scheme 2.

6 (Scheme 2). This enamine product was identical to that produced by isomerization of amine **7**.[12]

This type of pyrolysis also takes place in the injection port of a gas chromatograph. By varying the temperature of the injection port, the yields of enamine would vary. As the injection port temperature increased, the ratio of enamine to oxazine starting material would increase (see Table 1). Varying the ramping oven temperatures of the gas chromatograph starting at 70 °C did not significantly change these ratios. So these ratios can be used to predict the amount of enamine obtainable by pyrolysis. Using these indicators it can be seen from Table 1 that the *p*-methoxyphenyl, cyclohexyl, cyclopentyl and bicyclo[2.2.1]heptyl oxazines have the highest potential yields of enamines. This is important because it indicates that, by varying pyrolysis conditions, it should be possible to obtain much higher yields of enamine products than we actually did obtain in these limited experiments. Exploitation of the microwave



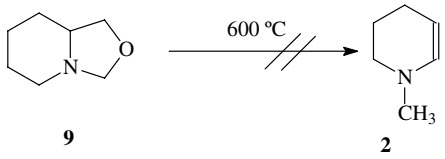
1 8 2

Scheme 3.

technique also shows great potential for increasing these yields significantly as shown by the example of the *p*-chlorophenyl substituted oxazine.

The mechanism for the formation of the enamine has as the first step the formation of azomethine ylide **8** resulting from the loss of acetaldehyde.[13] This is followed by a suprafacial [1,4]sigmatropic shift of a hydrogen to give enamine **2**[14] (Scheme 3).

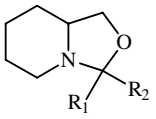
Pyrolysis of the bicyclo[4.3.0]nonane oxazines such as 3-oxa-1-azabicyclo[4.3.0]nonane[11] (**9**) did not produce an enamine product (Scheme 4). This was true of all of the oxazines shown in Table 2.



9 2

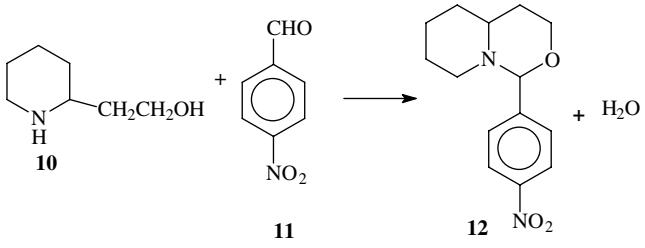
Scheme 4.

Table 2. Yields and physical properties of bicyclo[4.3.0]nonyl oxazines



R_1	R_2	% Yield	Boiling point °C (mmHg)
Ph[a]	H	74	93–97 (0.4)
p-ClPh[a]	H	82	100 (0.06)
p-O_2NPh[a]	H	28	64.5–65.5[b]
p-Me_2NPh[a]	H	63	60–62[b]
p-MeOPh[a]	H	79	133–138 (0.25)

[a] Satisfactory elemental analysis was obtained. Performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.
[b] Melting point.



10 11 12

Scheme 5.

A good method for synthesizing oxazines is the reaction of a secondary amine with an aldehyde or a ketone followed by nucleophilic attack of the intermediate iminium ion by an attached alcohol. This method forms the basis of the production of 2-substituted-3-oxa-1-azabicyclo[4.4.0]decanes[8,11,15,16] and 2-substituted-3-oxa-1-azabicyclo[4.3.0]nonanes.[11,17–19] For example when 2-piperidineethanol (**10**) was allowed to react with 4-nitrobenzaldehyde (**11**), 2-(4-nitrophenyl)-3-oxa-1-azabicyclo[4.4.0]decane[20] (**12**) was formed in a 95% yield (Scheme 5).

The simple 3-oxa-1-azabicyclo[4.4.0]decane (**1**) exists as an equilibrium mixture of the *trans* and O-inside *cis* isomers in the amounts of 97% *trans* and 3% O-inside *cis* at 203 K. This was based upon some low-temperature ^{13}C NMR spectroscopy measurements carried out by Crabb and Ingate.[21]

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10. Milestone ETHOS SYNTH Labstation with magnetic stirring, ATC-FO Automatic Temperature Control, glass reaction vial with Teflon cover and screw cap. It was held at 160 C for 1 h and 200 C for 1 3/4 h using 500 W power.
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