DIELS-ALDER REACTION OF 1,2,3-TRIAZINE WITH ALDEHYDE ENAMINE

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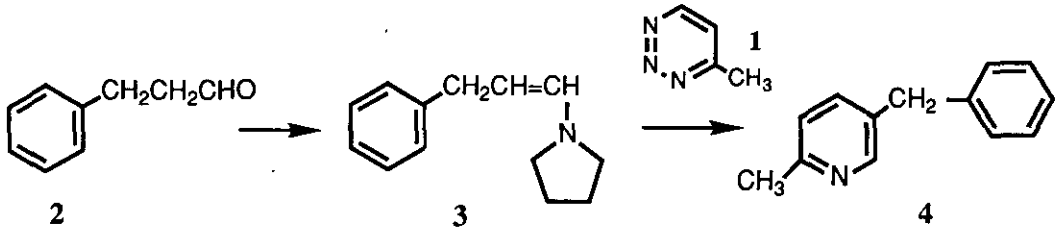
Abstract —— The Diels-Alder reaction of 4-methyl-1,2,3-triazine with several aldehyde enamines was carried out to afford 2,5-disubstituted pyridines. As an application of this method, we accomplished the synthesis of alkaloid, fusaric acid.

We have reported Diels-Alder reaction of 1,2,3-triazine with enamine for constructing pyridine ring.[1] This time, as an expansion of these works, we report the results obtained by the treatment of 4-methyl-1,2,3-triazine with aldehyde enamines. In addition, we describe the synthesis of alkaloid fusaric acid by the application of this result.



The mixture of 4-methyl-1,2,3-triazine (**1**) and phenylpropionaldehyde enamine (**3**) in dry $CHCl_3$ was heated in a sealed glass tube at 90° for 2 h to give 5-benzyl-2-methylpyridine (**4**) in 1-2% yields. In contrast to this, when Lewis acids were present under the same reaction conditions, the yield of the preparation of 5-benzyl-2-methylpyridine (**4**) became better. The yields of the pyridine (**4**) in the presence of some Lewis acids are summarized in Table I.

Table I The Yields of the Preparations of 5-Benzyl-2-methylpyridine (4)

	Yield (%)				
	$ZnBr_2$	$AlCl_3$	BF_3·etherate	$TiCl_4$	nafion*[1]
0.1 eq.	23.0	13.5	14.6	25.0 (0.25eq.)	20.0
1 eq.	40.0	trace	28.1	13.4	17.0
1.5 eq.	43.2	—*[2]	30.0	—	—
3 eq.	28.5	—	13.7	—	—

*[1] Nafion NR50(beads) purchased from Aldrich
*[2] No experience

We also ran the reaction in several other aldehyde enamines, and the results in the presence of Lewis acids are summerized in Table II. The reaction of triazine with aldehyde enamines in the presence of $ZnBr_2$ resulted in the formation of pyridines in the best yield. Treatment of 1,2,3-triazine (**12**) with hexaldehyde enamine (**11**) by the same method gave 3-butylpyridine (**13**) in 82% yield [used $ZnBr_2$ (1.5 eq.)].

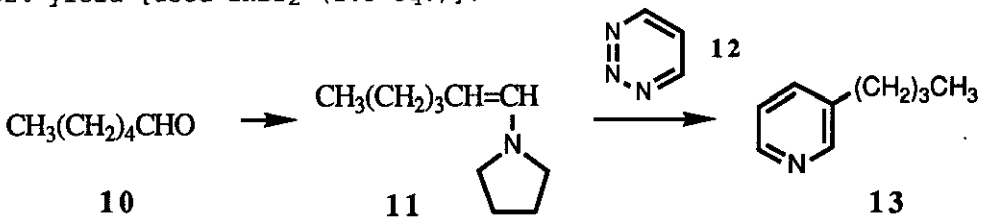
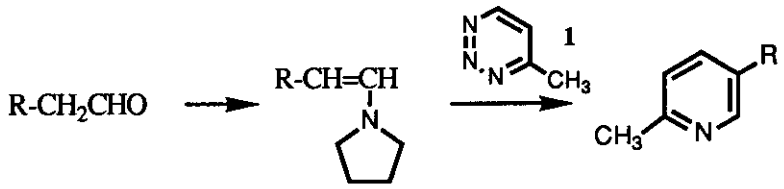


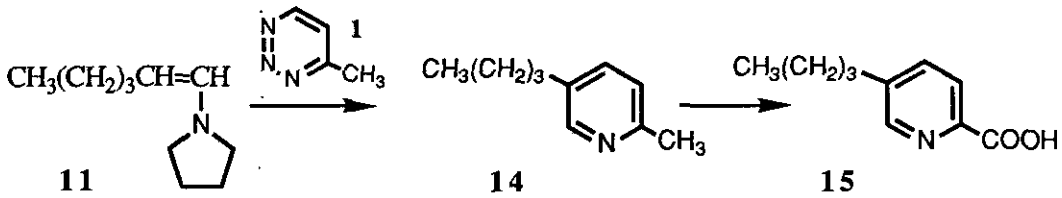
Table II The Yeilds of Pyridines from Aldehyde Enamines with Triazine



pyridine R=	Yield (%)					
	$ZnBr_2$ (1.5eq.)	$AlCl_3$ (0.1eq.)	BF_3·etherate (1eq.)	$TiCl_4$ (0.25eq.)	nafion (0.3eq.)	— *
$CH_3(CH_2)_2$ (5)	36.4	0	11.7	0	trace	0
$CH_3(CH_2)_5$ (6)	37.0	trace	11.0	5.0	27.0	0
$CH_3(CH_2)_{10}$ (7)	55.0	trace	3.0	5.5	15.0	0
C_6H_5 (8)	77.6	48.7	37.5	18.1	6.0	16.6
$C_6H_5CH_2$ (4)	43.2	13.5	28.0	25.0	19.8	trace
$C_6H_5CH_2CH_2$ (9)	32.0	5.0	trace	trace	12.0	0

* No catalyst

On the basis of the above results, we carried out the synthesis of alkaloid, fusaric acid.[2] Diels-Alder reaction of the pyrrolidine enamine (**11**) of hexaldehyde (**10**) with 4-methyltriazine (**1**) in dry $CHCl_3$ in the presence of $ZnBr_2$ (1.5 eq.) at 90° gave 5-butyl-2-methylpyridine (**14**) in 52.3% yield. Oxidation of the methyl group of the pyridine (**14**) with selenium oxide[3] afforded fusaric acid (**15**) in 40% yield, and its spectroscopic data showed good agreement with those described in the literature.[2]



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EXPERIMENTAL

^{1}H-Nmr spectra were determined in $CDCl_3$ with Me_4Si as the internal reference on a NEVA NV-21 instrument. Mass spectra were recorded on a JEOL JMS-01SG spectrometer. Ir spectra were measured on a Hitachi 270-30 spectrophotometer. Preparative thin layer chromatography was carried out on Kiesel gel $60F_{254}$ (Merck) with appropriate solvents.

General method for the Diels-Alder reaction of 1,2,3-triazine with enamines: A mixture of freshly prepared enamine (1.3 eq.) and 1,2,3-triazine (95 mg, 1 mmol) in dry $CHCl_3$ (2 ml) was heated in a sealed glass tube at 90° for 2 h in the presence of Lewis acid. The solvent was evaporated in vacuo, and the residue was chromatographed over silica gel using C_6H_6 and $CHCl_3$ as the eluent. The crude product was purified by preparative thin layer chromatography on silica gel ($CHCl_3$:MeOH=40:1) to give the corresponding pyridine as an oil.

5-Benzyl-2-methylpyridine (**4**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1610, 1580, 1570. Nmr δ: 2.50(3H, s, CH_3), 3.94 (2H, s, CH_2), 7.07 (1H, d, *J*=8 Hz, 3-H), 7.12-7.32 (5H, m), 7.36 (1H, dd, *J*=2 and 8 Hz, 4-H), 8.38 (1H, d, *J*=2 Hz, 6-H). Ms *m/z*: 183.1045 (M^+, calcd for $C_{13}H_{13}N$, 183.1046).

2-Methyl-5-propylpyridine (**5**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1620. Nmr δ: 0.96 (3H, t, *J*=6 Hz, CH_3), 1.16-1.88 (2H, m, CH_2), 2.57 (3H, s, 2-CH_3), 2.59 (2H, t, *J*=6 Hz, CH_2), 7.12 (1H, d, *J*=8 Hz, 3-H), 7.43 (1H, dd, *J*=2 and 8 Hz, 4-H), 8.38 (1H, d, *J*=2 Hz, 6-H). Ms *m/z*: 135.1040 (M^+, calcd for $C_9H_{13}N$, 135.1047).

5-Hexyl-2-methylpyridine (**6**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1610, 1570. Nmr δ: 0.82 (3H, t, *J*=6 Hz, CH_3), 1.02-1.74 (8H, m, CH_2X4), 2.18 (2H, t, *J*=6 Hz, CH_2), 2.46

(3H, s, 2-CH_3), 7.02 (1H, d, J=8 Hz, 3-H), 7.34 (1H, dd, J=2 and 8 Hz, 4-H), 8.26 (1H, d, J=2 Hz, 6-H). Ms m/z: 177.1518 (M^+, calcd for $C_{12}H_{19}N$, 177.1517).

2-Methyl-5-undecylpyridine (**7**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1610, 1570. Nmr δ: 0.88 (3H, t, J=7 Hz, CH_3), 1.15-1.86 (18H, m, CH_2X9), 2.52 (3H, s, 2-CH_3), 2.60 (2H, t, J=7 Hz, CH_2), 7.06 (1H, d, J=8 Hz, 3-H), 7.38 (1H, d, J=8 Hz, 4-H), 8.32 (1H, s, 6-H). Ms m/z: 247.2307 (M^+, calcd for $C_{17}H_{29}N$, 247.2299).

2-Methyl-5-phenylpyridine (**8**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1610, 1580. Nmr δ: 2.61 (3H, s, CH_3), 7.24 (1H, d, J=8 Hz, 3-H), 7.32-7.62 (5H, m), 7.78 (1H, dd, J=2.5 and 8 Hz, 4-H), 8.74 (1H, d, J=2.5 Hz, 6-H). Ms m/z: 169.0893 (M^+, calcd for $C_{12}H_{11}N$, 169.0891).

2-Methyl-5-phenethylpyridine (**9**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1610, 1570, 1500. Nmr δ: 2.45 (3H, s, CH_3), 2.88 (4H, s, CH_2X2), 7.08 (1H, d, J=8 Hz, 3-H), 7.10-7.32 (5H, m), 7.36 (1H, dd, J=2 and 8 Hz, 4-H), 8.32 (1H, d, J=2 Hz, 6-H). Ms m/z: 197.1215 (M^+, calcd for $C_{14}H_{15}N$, 197.1204).

3-Butylpyridine (**13**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1575. Nmr δ: 0.93 (3H, t, J=8 Hz, CH_3), 1.30-1.72 (4H, m, CH_2X2), 2.61 (2H, t, J=8 Hz, CH_2), 7.21 (1H, dd, J=5 and 8 Hz, 5-H), 7.50 (1H, dd, J=2 and 8 Hz, 4-H), 8.43 (1H, d, J=2 and 5 Hz, 6-H), 8.45 (1H, brs, 2-H). Ms m/z: 135.1059 (M^+, calcd for $C_9H_{13}N$, 135.1047).

5-Butyl-2-methylpyridine (**14**) Ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1604, 1570. Nmr δ: 0.92 (3H, t, J=7.5 Hz, CH_3), 1.33-1.70 (4H, m, CH_2X2), 2.51 (3H, s, 2-CH_3), 2.53 (2H, t, J=7.5 Hz, CH_2), 7.06 (1H, d, J=8 Hz, 3-H), 7.41 (1H, dd, J=2 and 8 Hz, 4-H), 8.32 (1H, d, J=2 Hz, 6-H). Ms m/z: 149.1212 (M^+, calcd for $C_{10}H_{15}N$, 149.1204).

Fusaric Acid (**15**) A suspension of 5-butyl-2-methylpyridine (**14**) (40 mg, 0.27 mmol) and selenium oxide (60 mg, 0.54 mmol) in pyridine (1 ml) was refluxed for 10 h with stirring. After it was filtered, the filtrate was washed with hot water and concentrated under reduced pressure. The residue

was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over, and evaporated to dryness to give the crude acid. The crude product was separated by preparative thin layer chromatography ($CHCl_3$:MeOH=25:1) to give fusaric acid. Yield: 19.5 mg (40%). mp 101-103° (MeOH) (lit.,[2]: mp 102.5-103.5°).

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