MODIFIED SYNTHESIS OF MONOCYCLIC 1,2,3-TRIAZINE AND CYCLOADDITION REACTION WITH ENAMINE : THE APPLICATION TO THE SYNTHESIS OF ALKALOIDS, TORTUOSAMINE, N-FORMYLTORTUOSAMINE AND N-ACETYLTORTUOSAMINE

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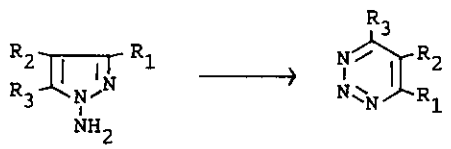
Abstract ——— Monocyclic 1,2,3-triazines were obtained by periodate oxidation of 1-aminopyrazoles in good reproducibilities and yields. The Diels-Alder reaction of 1,2,3-triazine with several enamines was carried out to afford 2,3-disubstituted pyridines. As an application of this method, we accomplished the synthesis of alkaloids, tortuosamine, N-formyltortuosamine and N-acetyltortuosamine.

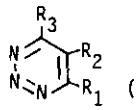
In our recent reports,[1] 1,2,3-triazines have been shown to participate in Diels-Alder reaction with enamines. The problem, however, was the poor synthetic yield and reproducibility of the monocyclic 1,2,3-triazines. Especially, synthesis of unsubstituted 1,2,3-triazine (IIa) was difficult.[2a,b] On the other hand, 1,2,3-triazines (II) were synthesized by oxidizing 1-aminopyrazoles (I) with metallic oxidizing reagents. During our studies on the oxidation of I, we found that the oxidation with sodium periodate or potassium periodate gave II not only in improved yield, but in good reproducibility. We could obtain IIa in 46% yield. The results obtained are summarized in Table I.[3]



(Ia-e) (IIa-e)

a : R_1=R_2=R_3=H
b : R_1=CH_3, R_2=R_3=H
c : R_1=R_3=H, R_2=CH_3
d : R_1=R_3=CH_3, R_2=H
e : R_1=R_2=R_3=CH_3

Table I

	 (IIa-e)	$NaIO_4$	KIO_4
		yield (%)	
a	$R_1=R_2=R_3=H$	46	32
b	$R_1=CH_3$, $R_2=R_3=H$	82	80
c	$R_1=R_3=H$, $R_2=CH_3$	82	82
d	$R_1=R_3=CH_3$, $R_2=H$	93	84
e	$R_1=R_2=R_3=CH_3$	92	81

As mentioned previously, we have already reported the Diels-Alder reaction of 4-methyl-1,2,3-triazine with enamines.[1] This time, we investigated the cycloaddition reaction of each 1,2,3-triazines (IIa-e) with several enamines. A mixture of 1,2,3-triazine and pyrrolidine enamine in dry $CHCl_3$ or o-dichlorobenzene was heated in a sealed glass tube at 100~220°C for 1~2 h. The crude products were separated by preparative thin layer chromatography on silica gel. The results are summarized in Table II.

Table II : Cycloaddition reaction of 1,2,3-triazines with pyrrolidine enamines

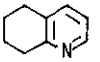
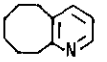
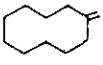
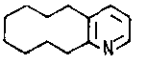
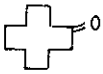
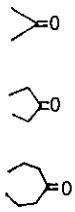
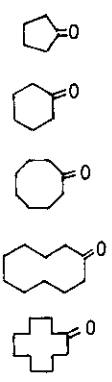
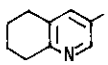
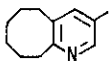
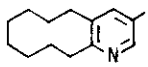
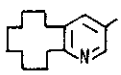
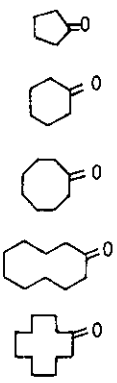
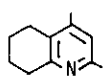
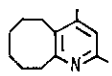
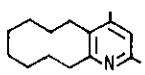
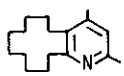
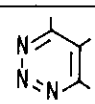
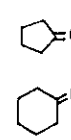
triazine	ketone	reaction condition	product (III)	yield (%)
 (IIa)		A]	III$_1$ 	20
			2 	22
			3 	38
			4 	35
			5 	68
			6 	14
				32

Table II : continued

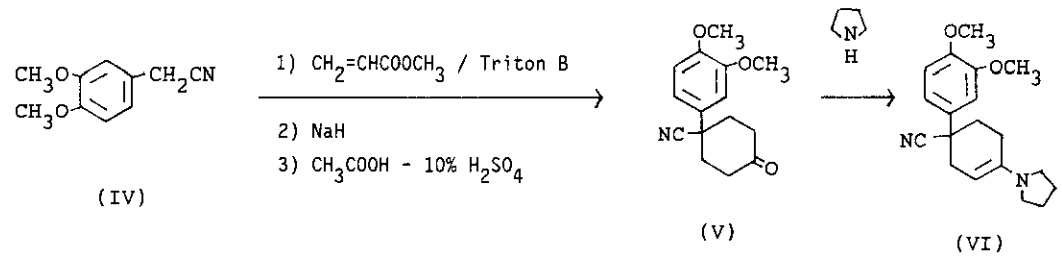
 (IIb)		A]	III_8 	trace
			9 	16
			10 	15
 (IIc)		A]	11 	60
			12 	38
			13 	65
			14 	24
			15 	54
 (IId)		A]	recovered triazine	–
		B]	16 	12
			17 	27
			18 	18
			19 	16
 (IIe)		A]	recovered triazine	–
		B]	recovered triazine	–

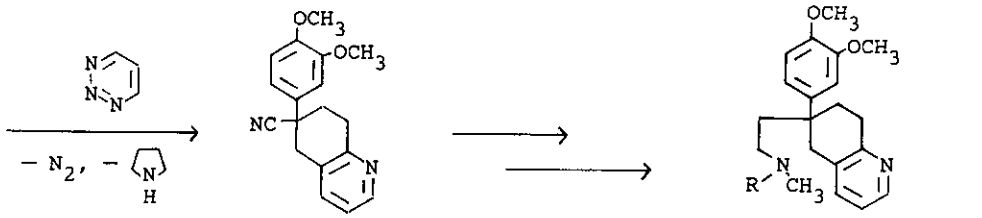
A] : in dry $CHCl_3$, 100∼120°C, 2 h

B] : in dry o-dichlorobenzene, 200∼220°C, 1 h

The reaction of unsubstituted triazine (IIa) and monosubstituted triazines (IIb,c) proceeded under relatively mild conditions. Only unreactive triazines were recovered as di- (IId) and trisubstitutes (IIe) under the same conditions. Under the stronger conditions, disubstitute (IId) underwent the cycloaddition reaction except for IIe. In conclusion, compounds (IIa,b,c) are sufficiently electron deficient to participate in the inverse electron demand Diels-Alder reaction. On account of the more alkylated triazine nuclei, IId and e decrease the nucleophlic character of the azadiene, causing a poor reaction.

In addition, we report the synthesis of the quinoline derivative (VII) which is the key intermediate of alkaloids, tortuosamine (VIII), N-formyltortuosamine (IX) and N-acetyltortuosamine (X). 1-(3',4'-Dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (V), which was synthesized from 3,4-dimethoxyphenylacetonitrile (IV), to give pyrrolidine enamine (VI) by a standard procedure. VI was immediately treated with 1,2,3-triazine (IIa) in dry $CHCl_3$ in a sealed glass tube at 100∿110°C (bath temp.) for 3 h. The crude products obtained were separated by silica gel column chromatography to give the quinoline derivative (VII) in 13% yield. The synthesis of each alkaloid (VIII,IX,X) from VII had been achieved by our groups.[4a,b]





(VIII) R=H
(IX) R=CHO
(X) R=$COCH_3$

EXPERIMENTAL

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

General method of preparation of 1,2,3-triazines :

To an ice-cold solution of 0.01 mol of pyrazole in 30 ml of CH_2Cl_2 and 10 ml of water was added 0.02 mol of solid sodium periodate or potassium periodate with stirring. The reaction mixture was stirred overnight at 0∼5°C and then extracted repeatedly with $CHCl_3$. The $CHCl_3$ solution was dried over sodium sulfate, concentrated and purified by recrystallization or column chromatography on silica gel.

General procedure for the Diels-Alder reaction of 1,2,3-triazines with enamines :

Method A: A mixture of freshly prepared enamine (1.2∼1.4 equiv) and 1,2,3-triazine (1 mmol) in dry $CHCl_3$ (2 ml) was heated in a sealed glass tube at 100∼120°C for 2 h. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography using C_6H_6 and $CHCl_3$ as the eluent. 2,3-Disubstituted pyridines were obtained from the fraction eluted with C_6H_6-$CHCl_3$ (1:1). The crude products were separated by preparative thin layer chromatography on silica gel.

Method B: A mixture of freshly prepared enamine (1.2∼1.4 equiv) and 1,2,3-triazine (1 mmol) in dry o-dichlorobenzene (2 ml) was heated in a sealed glass tube at 200∼220°C for 1 h. The method of purification was same as that previously the described.

3-Ethyl-6-methyl-2-propylpyridine (III_{10}) : $\nu_{max}^{CHCl_3}$: 1595cm^{-1}; ms m/z : 163.1365 (M^+, calcd for $C_{11}H_{17}N$, 163.1360); nmr δ : 1.00 (3H, t, J=7Hz, Me), 1.20 (3H, t, J=7Hz, Me), 2.49 (3H, s, 6-Me), 6.92 (1H, d, J=8Hz, 5-H), 7.33 (1H, d, J=8Hz, 4-H)

3-Methylcyclodeca[b]pyridine (III_{14}) : $\nu_{max}^{CHCl_3}$: 1600cm^{-1}; ms m/z : 203.1676 (M^+, calcd for $C_{14}H_{21}N$, 203.1673); nmr δ : 2.28 (3H, s, Me), 7.26 (1H, s, 4-H), 8.28 1H, s, 2-H)

3-Methylcyclododeca[b]pyridine (III_{15}) : $\nu_{max}^{CHCl_3}$: 1600cm^{-1}; ms m/z : 231.1977 (M^+, calcd for $C_{16}H_{25}N$, 231.1985); nmr δ : 2.26 (3H, s, Me), 7.26 (1H, d, J=2Hz, 4-H), 8.22 (1H, d, J=2Hz, 2-H)

2,4-Dimethylcycloocta[b]pyridine (III_{17}) : $\nu_{max}^{CHCl_3}$: 1605cm^{-1}; ms m/z : 189.1515 (M^+, calcd for $C_{13}H_{19}N$, 189.1516); nmr δ : 2.26 (3H, s, 4-Me), 2.45 (3H, s, 2-Me), 6.79 (1H, s, 3-H)

2,4-Dimethylcyclodeca[b]-pyridine (III_{18}) : $\nu_{max}^{CHCl_3}$: 1600cm^{-1}; ms m/z : 217.1829 (M^+, calcd for $C_{15}H_{23}N$, 217.1829); nmr δ : 2.28 (3H, s, 4-Me), 2.45 (3H, s, 2-Me), 6.77 (1H, s, 3-H)

2,4-Dimethylcyclododeca[b]pyridine (III_{19}) : $\nu_{max}^{CHCl_3}$: 1600cm^{-1}; ms m/z : 245.2137

(M^+, calcd for $C_{17}H_{27}N$, 245.2141); nmr δ : 2.28 (3H, s, 4-Me), 2.44 (3H, s, 2-Me), 6.77 (1H, s, 3-H)

Enamination of 1-(3',4'-dimethoxyphenyl)-4-oxocyclohexanecarbonitrile (V) :
A mixture of ketone (V, 1 g), excess pyrrolidine (1.5 ml), a small amount of p-toluenesulfonic acid, 10 ml of C_6H_6 and 6 ml of hexane was refluxed for 3 h using a Dean-Stark trap for water separation. The solution was evaporated to dryness in vacuo to give 1.17 g of enamine (VI) as a solid. This crude enamine was immediately used in the next step without further purification.

6-(3',4'-Dimethoxyphenyl)-5,6,7,8-tetrahydro-6-quinolinecarbonitrile (VII)[4a] :
A mixture of 1,2,3-triazine (IIa, 0.243 g) and crude enamine (VI, 1.17 g) in dry $CHCl_3$ (6 ml) was heated in a sealed glass tube at 100∼110°C (bath temp.) for 3 h. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography. From the first fraction eluted with C_6H_6, 589 mg (61%) of hydrolysis product (V) was recovered. From the fraction eluted with C_6H_6-$CHCl_3$ (1:1), 99 mg (13%) of tetrahydroquinoline (VII) and 24 mg (10%) of 1,2,3-triazine (IIa were obtained. The mixture of (VII) and (IIa) was separated by preparative thin layer chromatography on silica gel ($CHCl_3$:MeOH=50:1). (VII) : mp 117-118°C (Et_2O); ms m/z : 294(M^+); $\nu_{max}^{CHCl_3}$: 2230cm^{-1}(CN); nmr δ : 2.32-2.60 (2H, m), 3.06-3.56 (4H, m), 3.90 and 3.91 (6H, each s, 2xOMe), 6.87-7.06 (3H, m, aromatic-H), 7.14 (1H, dd, J=8 and 5Hz, 3-H), 7.45 (1H, dd, J=8 and 2Hz, 4-H), 8.48 (1H, dd, J=5 and 2Hz, 2-H)

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4. a) J. Koyama, T. Sugita, Y. Suzuta, and H. Irie, Heterocycles, 1981, 16, 969. b) J. Koyama, T. Sugita, K. Tagahara, Y. Suzuta, and H. Irie, Heterocycles, 1984, 22, 1973.

Received, 15th May, 1989