THE EFFECTS OF SOLVENT AND TEMPERATURE ON THE ORIENTATION OF CYCLOADDITION REACTION OF 1,2,3-TRIAZINE WITH ENAMINES : ITS APPLICATION TO THE SYNTHESIS OF ALKALOIDS, ONYCHINE AND 6-METHOXYONYCHINE

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Abstract ——— 4-Methyl-1,2,3-triazine was treated with several enamines in chloroform to afford 2,5,6-trisubstituted pyridines. In each case, cycloaddition occurs N-3/C-6 of the 1,2,3-triazine nucleus. On the other hand, when high boiling solvent was employed, cycloaddition took place involving the N-3/C-6 cycloadduct and N-1/C-4 cycloadduct. As application of synthetic method, we accomplished the synthesis of alkaloids, onychine and 6-methoxyonychine.

Recently we have reported that 1,2,3-triazine participates in inverse electron demanded Diels-Alder reaction with enamines[1]. This time, as an expansion of these works, we investigated the effects of solvent and temperature on directionality of cycloaddition. In addition, we report the synthesis of alkaloids onychine and 6-methoxyonychine by application of this result. A mixture of 4-methyl-1,2,3-triazine and several enamines in dry $CHCl_3$ was heated in a sealed glass tube at 60-150°C for 0.5-19 h to give 2,5,6-trisubstituted pyridines (path A). In contrast to this, when high boiling solvents were employed, cycloaddition reaction of 4-methyl-1,2,3-triazine with pyrrolidine enamine of cyclooctanone took place via path A and path B, producing the N-3/C-6 and N-1/C-4 cycloadducts, respectively. The results are summarized in Table.

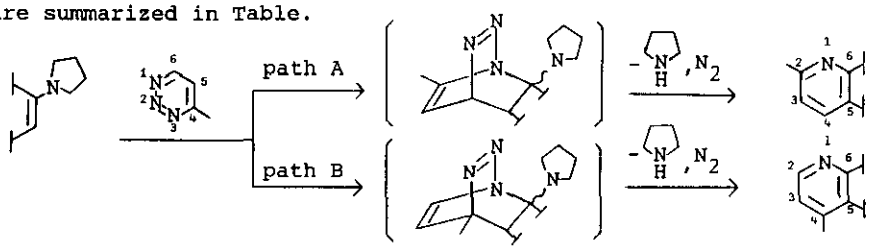
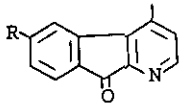


Table Cycloaddition reaction of 4-methyl-1,2,3-triazine with pyrrolidine enamine of cyclooctanone

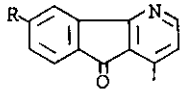
solvent	reaction conditions	products a) : a')	yield (%) a) + a')
dichloromethane	60°C, 5h	100 : 0	24.8
chloroform	60°C, 19h	100 : 0	44.0
	100°C, 2h	100 : 0	69.0
benzene	100°C, 1.5h	100 : 0	11.4
xylenes	150°C, 37 min.	64 : 36	17.4
chlorobenzene	150°C, 35 min.	75 : 25	18.1
bromobenzene	180°C, 30 min.	49 : 51	19.3
o-dichlorobenzene	200°C, 30 min.	43 : 57	23.1
p-dichlorobenzene	220°C, 10 min.	45 : 55	19.0

On the basis of the above results, we carried out the synthesis of alkaloids, onychine and 6-methoxyonychine. In 1976, Maia and his co-workers isolated the novel alkaloid onychine from Onychopetalum amazonicum (Annonaceae)[2]. Its structure was assigned 4-methyl-1-azafluoren-9-one (1). In 1979, we synthesized both 4-methyl-1-azafluoren-9-one (1) and its structural isomer, 1-methyl-4-azafluoren-9-one (2), and we suggested that the structure of onychine should be revised to (2)[3]. In spite of this result, the erroneous structure was retained till several years later[4]. In recent reports[5], however, these structures were proved to be 1-methyl-4-azafluoren-9-one (2) and 6-methoxy-1-methyl-4-azafluoren-9-one (4) based on nmr studies and the direct comparsion of the synthetic products with naturally occurring alkaloids.



(1) R=H

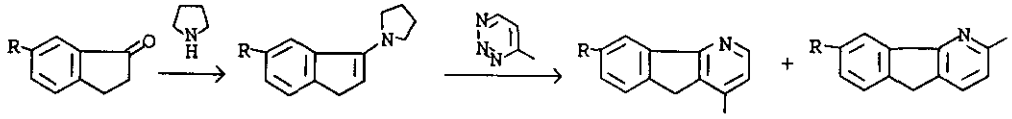
(3) R=OCH_3



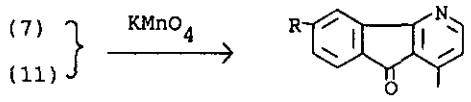
(2) R=H

(4) R=OCH_3

Onychine (2) was synthesized according to the following equation. Diels-Alder reaction of pyrrolidine enamine (6) of 1-indanone (5) with 4-methyl-1,2,3-triazine in dry o-dichlorobenzene in a sealed glass tube at 150-160°C (bath temp.) gave 1-methyl-4-azafluorene (7) and 3-methyl-4-azafluorene (8). Oxidation of the azafluorene (7) with potassium permanganate afforded onychine (2) in 72% yield.



(5) R=H (6) R=H (7) R=H (8) R=H
(9) R=OCH_3 (10) R=OCH_3 (11) R=OCH_3 (12) R=OCH_3



(2) R=H
(4) R=OCH_3

In addition, we synthesized 6-methoxyonychine (4). 6-Methoxyindanone (9), prepared from 3-(4-methoxyphenyl)propionic acid, was treated with pyrrolidine. Cycloaddition reaction of enamine (10) with 4-methyl-1,2,3-triazine in dry o-dichlorobenzene at 180°C (bath temp.) for 5 min gave 6-methoxy-1-methyl-4-azafluorene (11) and 6-methoxy-3-methyl-4-azafluorene (12). Oxidation of (11) with potassium permanganate gave 6-methoxyonychine (4) in 90% yield. These compounds were identified by direct comparsion with synthesized authentic sample of onychine and 6-methoxyonychine.[3,6]

EXPERIMENTAL

^{1}H-Nmr spectra were determined in $CDCl_3$ with Me_4Si as 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 spectrometer. Preparative thin layer chromatography was carried out on Kieselgel 60 F_{254} (Merck) with appropriate solvents.

General procedure for the Diels-Alder reaction of 4-methyl-1,2,3-triazine with enamines : A mixture of freshly prepared enamine (1.2~1.4 equiv) and 4-methyl-1,2,3-triazine in appropriate dry solvents was heated in a seald glass tube at 60-220°C (bath temp.) for 10 min-19 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 an eluent. The crude products were separated by preparative thin layer chromatography on silica gel.

1-Methyl-4-azafuluorene (7) and 3-Methyl-4-azafuluorene (8) :

A mixture of 4-methyl-1,2,3-triazine (100mg) and pyrrolidine enamine of 1-indanone (275mg) in dry o-dichlorobenzene (1ml) was heated in a sealed glass tube at 150-160°C (bath temp.) for 15 min. The crude products were separated by thin layer chromatography on silica gel, using the system C_6H_6:Et_2O (70:50), to afford 1-methyl-4-azafuluorene (7) (8mg, 4.2%) and 3-methyl-4-azafuluorene (8) (30mg, 16%).

(7) : Ms m/z : 181.0912(M^+, calcd for $C_{13}H_{11}N$, 181.0891) ; nmr($CDCl_3$) δ : 2.38(3H, s, 1-CH_3), 3.71(2H, s, 9-CH_2), 7.03(1H, d, J=5Hz, 2-H), 8.46(1H, d, J=5Hz, 3-H).

(8) : Ms m/z : 181.0881(M^+, calcd for $C_{13}H_{11}N$, 181.0891) ; nmr($CDCl_3$) δ : 2.60(3H, s, 3-CH_3), 3.70(2H, s, 9-CH_2), 7.03(1H, d, J=8Hz, 2-H), 7.68(1H, d, J=8Hz, 1-H).

6-Methoxy-1-methyl-4-azafluorene (11) and 6-Methoxy-3-methyl-4-azafluorene (12) :

(11) : 6% ; ms m/z : 211.0977(M^+, calcd for $C_{14}H_{13}NO$, 211.0996) ; nmr($CDCl_3$) δ : 2.41(3H, s, 1-CH_3), 3.70(2H, s, 9-CH_2), 3.90(3H, s, OCH_3), 7.02(1H, d, J=5Hz, 2-H), 8.48(1H, d, J=5Hz, 3-H).

(12) : 12% ; ms m/z : 211.1005(M^+, calcd for $C_{14}H_{13}NO$, 211.0996) ; nmr($CDCl_3$) δ: 2.63(3H, s, 3-CH_3), 3.70(2H, s, 9-CH_2), 3.86(3H, s, OCH_3), 7.03(1H, d, J=8Hz, 2-H), 7.65(1H, d, J=8Hz, 1-H).

Onychine (2) : To a solution of 1-methyl-4-azafuluorene (7) (8mg) in acetone (1ml), potassium permanganate (24mg) and magnesium sulfate (16mg) were added and the mixture was stired at room temperature untill tlc on slica gel indicated the disappearance of the starting azafuluorene. Excess potassium permanganate was decomposed by adding a smoll amount of ethanol. The reaction mixture was filtered and the filtrate was evaporated. The crude product was purified by preparative thin layer chromatography on silica gel to afford yellow crystal in 72% yield. $\nu_{max}^{CHCl_3}$: 1710, 1600, 1575cm^{-1} ; ms m/z : 195.0684(M^+, calcd for $C_{13}H_9NO$, 195.0684) ; nmr ($CDCl_3$) δ : 2.64(3H, s, 1-CH_3), 6.99(1H, d, J=5Hz, 2-H), 7.44(1H, m, 6 or 7-H), 7.61(1H, m, 7 or 6-H), 7.72(1H, m, 5 or 8-H), 7.85(1H, m, 8 or 5-H), 8.43(1H, d, J=5Hz, 3-H).

6-Methoxyonychine : 90% yield ; $\nu_{max}^{CHCl_3}$: 1710, 1610, 1575cm^{-1} ; ms m/z : 225.0802 (M^+, calcd for $C_{14}H_{11}NO_2$, 225.0814) ; nmr($CDCl_3$) δ : 2.58(3H, s, 1-CH_3), 3.87(3H, s, OCH_3), 6.87(1H, dd, J=8 and 3Hz, 7-H), 6.95(1H, d, J=5Hz, 2-H), 7.35(1H, d, J=3Hz, 5-H), 7.63(1H, d, J=8Hz, 8-H), 8.35(1H, d, J=5Hz, 3-H).

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