THE ALTERNATIVE SYNTHESIS OF ISOQUINOLINE NUCLEUS USING THE THERMAL ELECTROCYCLIC REACTION OF 1-AZAHEXA-1,3,5-TRIENE SYSTEM[1]

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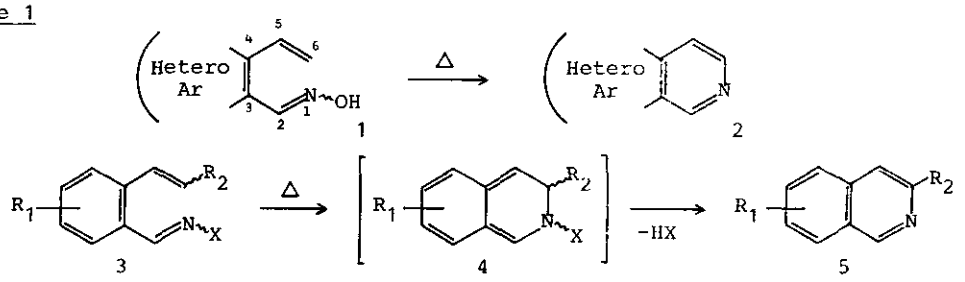
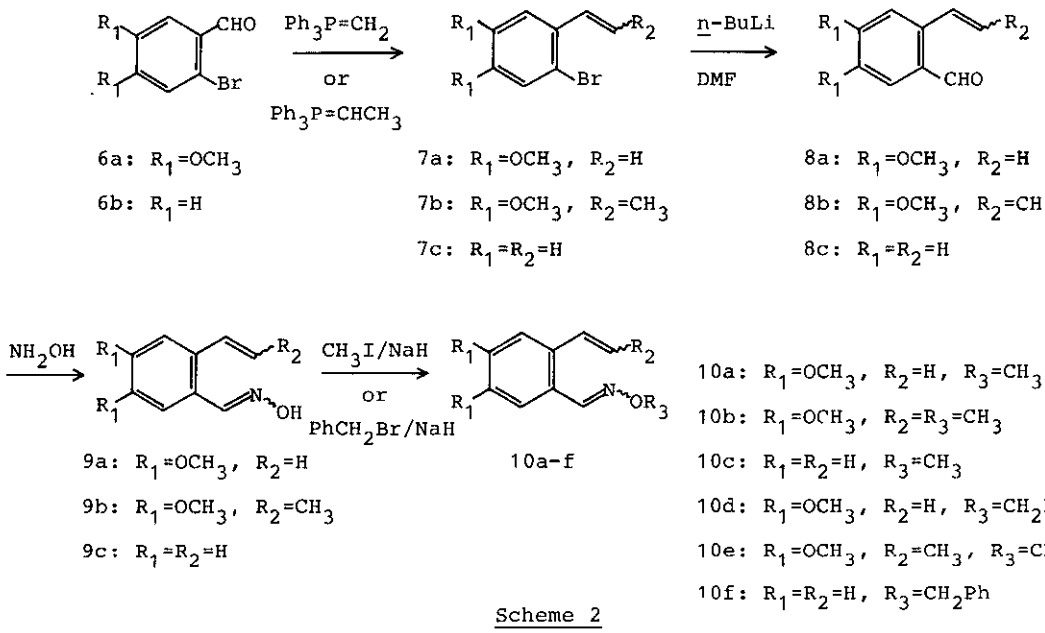
Abstract——The thermal electrocyclic reaction of 2-alkenylbenzaldoximes or their derivatives having conjugated 1-azahexatriene system in o-dichlorobenzene gave isoquinolines in moderate to good yields except the reaction of unsubstituted 2-alkenylbenzaldoxime and its oxime ethers.

In the course of our study, we previously reported the syntheses of fused pyridine ring systems (2) by the thermal electrocyclic reaction of monoazahexa-1,3,5-triene system (1) including one double bond of the heteroaromatics.[2] We have recently applied this thermal cyclization of 1-azahexa-1,3,5-triene system (3) to the construction of isoquinoline nucleus of aaptamine and succeeded in its total synthesis.[3] We now describe here the general use of this methodology for the preparation of the isoquinoline nucleus (5) as shown in Scheme 1.

Scheme 1





6a: R_1=OCH_3
6b: R_1=H

7a: R_1=OCH_3, R_2=H
7b: R_1=OCH_3, R_2=CH_3
7c: R_1=R_2=H

8a: R_1=OCH_3, R_2=H
8b: R_1=OCH_3, R_2=CH_3
8c: R_1=R_2=H

9a: R_1=OCH_3, R_2=H
9b: R_1=OCH_3, R_2=CH_3
9c: R_1=R_2=H

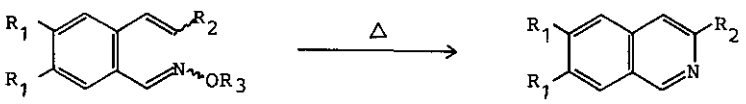
10a-f

10a: R_1=OCH_3, R_2=H, R_3=CH_3
10b: R_1=OCH_3, R_2=R_3=CH_3
10c: R_1=R_2=H, R_3=CH_3
10d: R_1=OCH_3, R_2=H, R_3=CH_2Ph
10e: R_1=OCH_3, R_2=CH_3, R_3=CH_2Ph
10f: R_1=R_2=H, R_3=CH_2Ph

Scheme 2

The starting iminostyrenes (9 and 10) were prepared from o-bromobenzaldehydes (6a and 6b) as follows. Wittig reaction of 6 with methylenetriphenylphosphorane or ethylidenetriphenylphosphorane gave the o-bromostyrenes (7a; 91%), (7b; 77%, a mixture of E/Z) and (7c; 42%), respectively. Subsequent treatment of 7a-c with n-BuLi at -78°C followed by addition of dimethylformamide afforded the benzaldehydes (8a-c; 48-94%). Conversion of the aldehydes (8a-c) into the oximes (9a-c) with hydroxylamine hydrochloride and sodium acetate in ethanol provided the benzaldoximes (9a-c; 65-92%). Alkylation of the oximes (9a-c) with methyl iodide/sodium hydride or benzyl bromide/sodium hydride gave the oxime O-alkyl ethers (10a-f; 56-96%) as shown in Scheme 2. Thermal electrocyclic reaction of the substituted iminostyrenes (9) or (10) in o-dichlorobenzene or diphenyl ether under reflux provided the desired isoquinolines (11) in moderate to good yields. However, the reaction of the unsubstituted iminostyrenes (9c), (10c) or (10f) did not proceed smoothly in o-dichlorobenzene as shown in Table 1. A mechanism that rationalizes the formation of the isoquinolines is shown in Scheme 1. The iminostyrenes initially form the dihydroisoquinolines via the thermal electrocyclic reaction followed by the elimination of water, methanol or benzyl alcohol to form the corresponding isoquinolines. Finally, we found that the three types of leaving groups (OH, OCH_3 and OCH_2Ph) similarly play a role of the elimination, so that an each leaving group

Table 1[1)]



9a: R_1=OCH_3, R_2=R_3=H

9b: R_1=OCH_3, R_2=CH_3, R_3=H

9c: R_1=R_2=R_3=H

10a: R_1=OCH_3, R_2=H, R_3=CH_3

10b: R_1=OCH_3, R_2=R_3=CH_3

10c: R_1=R_2=H, R_3=CH_3

10d: R_1=OCH_3, R_2=H, R_3=CH_2Ph

10e: R_1=OCH_3, R_2=CH_3, R_3=CH_2Ph

10f: R_1=R_2=H, R_3=CH_2Ph

11a: R_1=OCH_3, R_2=H

11b: R_1=OCH_3, R_2=CH_3

11c: R_1=R_2=H

Iminostyrenes	Isoquinolines	Solvents		
		Xylene[2)]	o-Dichlorobenzene[3)]	Diphenyl Ether[4)]
9a	11a	81%	88%	87%
9b	11b	13%	49%	70%
9c	11c	—[5)]	16%	—[5)]
10a	11a	18%	76%	57%
10b	11b	20%	50%	60%
10c	11c	—[5)]	18%	—[5)]
10d	11a	21%	65%	50%
10e	11b	46%	66%	45%
10f	11c	—[5)]	39%	—[5)]

1) Isolated yield.

2) Refluxed for 48 h.

3) Refluxed for 12 h.

4) Refluxed for 0.5 h.

5) These conditions were not examined.

would be useful for the type of this reaction.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were measured with a JEOL *PMX-60Si* spectrometer. Mass spectra and high resolution mass spectra were recorded on Shimadzu GC-MS 6020 and 9020. E/Z ratios were determined by nmr spectra unless otherwise stated.

General Procedure for the Synthesis of the Styrenes (7)——A solution of n-BuLi (1.5 M in hexane solution, 112 mmol) was added to an ice-cooled suspension of methyltriphenylphosphonium bromide or ethyltriphenylphosphonium bromide (112 mmol) in dry THF (100 ml) under N_2. After completion of ylid formation (30 min), a solution of the aldehydes (6; 100 mmol) in dry THF (100 ml) was added to this ylid and the stirring was continued at room temperature for 14 h. This mixture was worked up with brine, and extracted with benzene. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 250 g) using EtOAc/hexane (2:98) to give the styrenes (7).

2-Bromo-4,5-dimethoxystyrene (7a): 91%, bp 140-142°C/15 torr (lit.[4], bp 142°C/18 torr). ^{1}H-Nmr ($CDCl_3$) δ: 3.83(3H, s), 3.86(3H, s), 5.18(1H, dd, J=10 and 2Hz), 5.48(1H, dd, J=17 and 2Hz), 6.90(1H, s), 6.97(1H, s), 6.66-7.17(1H, m). Ms: m/z 244(M^++2), 242(M^+). Anal. Calcd for $C_{10}H_{11}O_2Br$: C, 49.41; H, 4.56. Found: C, 49.30; H, 4.60.

2-Bromo-4,5-dimethoxy-(1-propenyl)benzene (7b): 77%(E/Z=1:1). bp 142-143°C/1 torr (lit.[4], bp 140°C/0.5 torr). ^{1}H-Nmr ($CDCl_3$) δ: 1.73(1.5H, dd, J=8 and 2Hz), 1.88 (1.5H, dd, J=6 and 2Hz), 3.88(6H, s), 5.63-6.83(1H, m), 6.93(1H, s), 7.03(1H, s), 7.37-7.90(1H, s). Ms: m/z 258(M^++2), 256(M^+). Anal. Calcd for $C_{11}H_{13}O_2Br$: C, 51.38; H, 5.10. Found: C, 51.35; H, 5.09.

2-Bromostyrene (7c): 42%, bp 105°C/20 torr (lit.[5], bp 105°C/20 torr). ^{1}H-Nmr ($CDCl_3$) δ: 5.28(1H, dd, J=10 and 2Hz), 5.62(1H, dd, J=17 and 2Hz), 6.78-7.55(5H, m). Ms: m/z 184(M^++2), 182(M^+).

General Procedure for the Synthesis of the Benzaldehydes (8)——A solution of n-BuLi (1.5 M in hexane solution, 80.3 mmol) was added to a cooled (-78°C) solution of the bromobenzene derivatives (7; 80 mmol) in dry THF (100 ml) under N_2. The stirring was

continued at this temperature for 30 min and a solution of DMF (81.4 mmol) in dry THF (30 ml) was added dropwise. After keeping the temperature for 1 h, the solution was stirred at room temperature for 1 h and then worked up with brine. The mixture was extracted with $CHCl_3$ and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 130 g) using EtOAc/hexane (1:9) to give the aldehydes (8).

2-Ethenyl-4,5-dimethoxybenzaldehyde (8a): 94%, mp 52-54°C (EtOAc/hexane) (lit.[4], mp 54-55°C). Ir_{max}^{KBr} cm^{-1}: 1665(CHO). Ms: m/z 192(M^+).

4,5-Dimethoxy-2-(1-propenyl)benzaldehyde (8b): 48%(E/Z=1:1), viscous oil. ^{1}H-Nmr ($CDCl_3$) δ: 1.65(1.5H, dd, J=7 and 2Hz), 1.90(1.5H, dd, J=5 and 2Hz), 3.87(3H, s), 3.90(3H, s), 5.67-6.28(1H, m), 6.57(0.5H, s), 6.77(0.5H, s), 6.73-7.20(1H, m), 7.22 (0.5H, s), 7.28(0.5H, s), 9.90(0.5H, s), 10.05(0.5H, s). Ms: m/z 206(M^+). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.35. Found: C, 70.01; H, 6.40.

2-Ethenylbenzaldehyde (8c): 69%, bp 103-105°C/10 torr. ^{1}H-Nmr ($CDCl_3$)[6] δ: 5.43(1H, dd, J=7 and 2Hz), 5.67(1H, dd, J=14 and 2Hz), 7.03-8.17(5H, m), 10.18(1H, s). Ms: m/z 132(M^+). Anal. Calcd for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.88; H, 6.05.

General Procedure for the Synthesis of the Benzaldoximes (9)——A solution of the benzaldehydes (8; 20 mmol), $NH_2OH \cdot HCl$ (28.7 mmol) and NaOAc (30.5 mmol) in EtOH (50 ml) was refluxed for 14 h. After removal of the solvent, the residue was extracted with $CHCl_3$, and extract was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 100 g) using $CHCl_3$ to give the benzaldoximes (9).

2-Ethenyl-4,5-dimethoxybenzaldoxime (9a): 85%, mp 121-123°C (EtOH). ^{1}H-Nmr ($CDCl_3$) δ: 3.83(3H, s), 3.87(3H, s), 5.17(1H, dd, J=10 and 2Hz), 5.40(1H, dd, J=17 and 2 Hz), 6.77(1H, s), 7.01(1H, dd, J=17 and 10Hz), 7.07(1H, s), 8.30(1H, s). Ms: m/z 207(M^+). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.70; H, 6.42; N, 6.88.

4,5-Dimethoxy-2-(1-propenyl)benzaldoxime (9b): 92%(E/Z=1:1), mp 116-120°C (EtOH). ^{1}H-Nmr ($CDCl_3$) δ: 1.65(1.5H, dd, J=7 and 2Hz), 1.87(1.5H, dd, J=5 and 2Hz), 3.90 (6H, s), 5.50-6.27(1H, m), 6.70(1H, s), 6.90(1H, s), 6.43-7.00(1H, m), 8.20(1H, s). Ms: m/z 221(M^+). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.83. Found: C, 65.30; H, 6.93; N, 6.43.

2-Ethenylbenzaldoxime (9c): 65%, mp 41.5-42.5°C (Et_2O). ^{1}H-Nmr ($CDCl_3$) δ: 5.36(1H, dd, J=10 and 2Hz), 5.58(1H, dd, J=16 and 2Hz), 7.02(1H, dd, J=16 and 10Hz), 7.13-

7.70(4H, m), 8.40(1H, s), 8.60(1H, br s). Ms: m/z 147(M^+). Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.40; H, 6.20; N, 9.51.

General Procedure for the Synthesis of the Oxime O-Alkyl Ethers (10)——A solution of the oximes (9; 10 mmol) in DMF (10 ml) was added dropwise to an ice-cooled suspension of NaH (60% in oil dispersion, 12 mmol) in DMF (5 ml) under N_2. After stirring for 30 min under ice-cooling, a solution of MeI (14 mmol) or $PhCH_2Br$ (14 mmol) in DMF (2 ml) was added dropwise, and then the mixture was stirred at room temperature for 1 h. The mixture was worked up with brine and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 20 g) using benzene to give the oxime O-alkyl ethers (10).

2-Ethenyl-4,5-dimethoxybenzaldoxime O-Methyl Ether (10a): 56%, mp 40-42°C. ^{1}H-Nmr ($CDCl_3$) δ: 3.87(6H, s), 3.92(3H, s), 5.22(1H, dd, J=12 and 2Hz), 5.45(1H, dd, J=18 and 2Hz), 6.83(1H, s), 6.85(1H, dd, J=18 and 2Hz), 7.17(1H, s), 8.23(1H, s). Ms: m/z 221(M^+). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.16; H, 6.81; N, 6.50.

4,5-Dimethoxy-2-(1-propenyl)benzaldoxime O-Methyl Ether (10b): 89%(E/Z=1:1), mp 31-39°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.60(1.5H, dd, J=7 and 2Hz), 1.87(1.5H, dd, J=6 and 2 Hz), 3.87(6H, s), 3.93(3H, s), 5.60-6.20(1H, m), 6.46-6.77(1H, s), 7.20(1H, s), 8.30(1H, s). Ms: m/z 235(M^+). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.40; H, 7.40; N, 6.10.

2-Ethenylbenzaldoxime O-Methyl Ether (10c): 69%, colorless liquid. ^{1}H-Nmr ($CDCl_3$) δ: 3.93(3H, s), 5.28(1H, dd, J=11 and 2Hz), 5.52(1H, dd, J=17 and 2Hz), 7.00(1H, dd, J=17 and 11Hz), 7.10-7.73(4H, m), 8.32(1H, s). Ms: m/z 161(M^+). High resolution Ms for $C_{10}H_{11}NO$: Calcd 161.0840. Found 161.0841.

2-Ethenyl-4,5-dimethoxybenzaldoxime O-Benzyl Ether (10d): 72%, mp 48-51°C. ^{1}H-Nmr ($CDCl_3$) δ: 3.85(6H, s), 5.15(2H, s), 5.30(1H, dd, J=18 and 2Hz), 5.33(1H, dd, J=12 and 2Hz), 6.85(1H, s), 6.97(1H, dd, J=18 and 12Hz), 7.20(1H, s), 7.33(5H, br s), 8.33(1H, s). Ms: m/z 297(M^+). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.83; H, 6.51; N, 4.70.

4,5-Dimethoxy-2-(1-propenyl)benzaldoxime O-Benzyl Ether (10e): 78%(E/Z=1:1), mp 63-65°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.66(1.5H, dd, J=8 and 2Hz), 1.87(1.5H, dd, J=6 and 2Hz), 3.87(6H, s), 5.15(2H, s), 5.73-6.07(1H, m), 6.43-6.80(1H, m), 6.77(1H, s), 7.20 (1H, s), 7.33(5H, br s), 8.17(1H, s). Ms: m/z 311(M^+). Anal. Calcd for $C_{19}H_{21}NO_3$:

C, 73.29; H, 6.80; N, 4.50. Found: C, 73.20; H, 6.91; N, 4.61.

2-Ethenylbenzaldoxime O-Benzyl Ether (10f): 96%, oil. ^{1}H-Nmr ($CDCl_3$) δ: 5.17(2H, s), 5.28(1H, dd, J=11 and 2Hz), 5.50(1H, dd, J=17 and 2Hz), 6.73-7.73(10H, m), 8.40(1H, s). Ms: m/z 237(M^+). High resolution Ms for $C_{16}H_{15}NO$: Calcd 237.1153. Found 237.1152.

General Procedure for the Thermal Electrocyclic Reaction of the Iminostyrenes (10) ——A mixture of oximes, oxime methyl ethers or oxime benzyl ethers (10; 0.5 mmol) in appropriate solvent was refluxed for an appropriate period as shown in Table 1. After removal of the solvent, the residue was purified by column chromatography (silica gel, 15-20 g) using MeOH/$CHCl_3$ (2:98). Yields were listed in Table 1.

6,7-Dimethoxyisoquinoline (11a): mp 91-93°C (Et_2O/hexane) (Lit.[7], mp 93°C). ^{1}H-Nmr ($CDCl_3$) δ: 4.00(6H, s), 7.00(1H, s), 7.13(1H, s), 7.45(1H, d, J=6Hz), 8.38(1H, d, J=6Hz), 9.00(1H, s). Ms: m/z 189(M^+). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.85; H, 5.90; N, 7.40.

6,7-Dimethoxy-3-methylisoquinoline (11b): mp 135-136°C (lit.[8], mp 135-136°C). ^{1}H-Nmr ($CDCl_3$) δ: 2.68(3H, s), 3.03(6H, s), 6.95(1H, s), 7.13(1H, s), 7.30(1H, s), 8.93(1H, s). Ms: m/z 203(M^+). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.80; H, 6.49; N, 6.95.

Isoquinoline (11c) was identified by the comparison with an authentic samples.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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