A FACILE AND ALTERNATIVE SYNTHESIS OF QUINOLINE NUCLEUS USING THERMAL CYCLIZATION OF 2-AZAHEXATRIENE SYSTEM GENERATED FROM 2-ALKENYL ACYLANILINE WITH $POCl_3$

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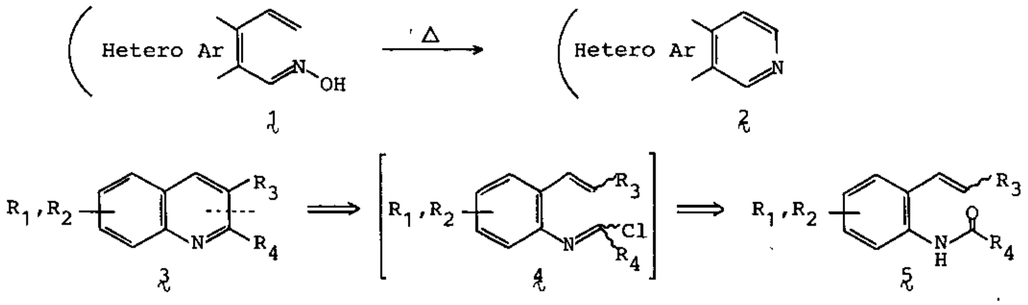
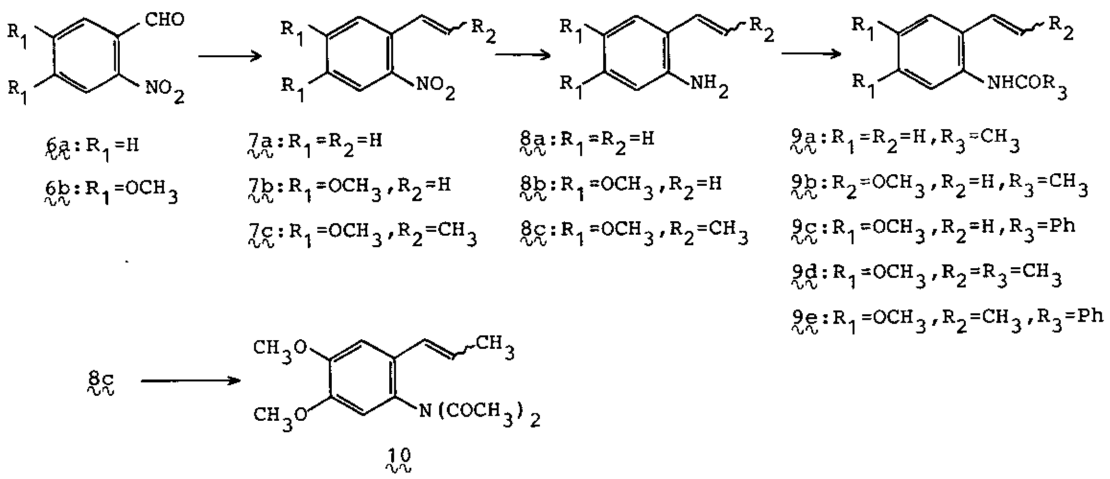
Abstract——The thermal cyclization of 2-alkenyl acylanilines with $POCl_3$ in toluene or xylene gave quinoline derivatives in good yield *via* 2-azahexatriene system *in situ*.

Since many quinolines occur in natural sources and have valuable pharmacological properties, much attention has been focused to the synthesis of substituted quinoline.[1] We have previously developed the synthesis of pyridine nucleus (2) fused to heteroaromatics such as thienopyridine, γ-carboline and β-carboline based on the thermal cyclization of 1-azahexatriene system (1)[2,3] as shown in Scheme 1. In this paper, we aimed to synthesize the quinoline nucleus using thermal cyclization of 2-azahexatriene system (4)[1b,c] derived from 2-alkenyl acylanilines (5) in retro synthetic pathway and found that this reaction proceeds smoothly in good yield.

For the synthesis of 2-alkenyl acylaniline (9) as a precursor of 2-azahexatriene



Scheme 1

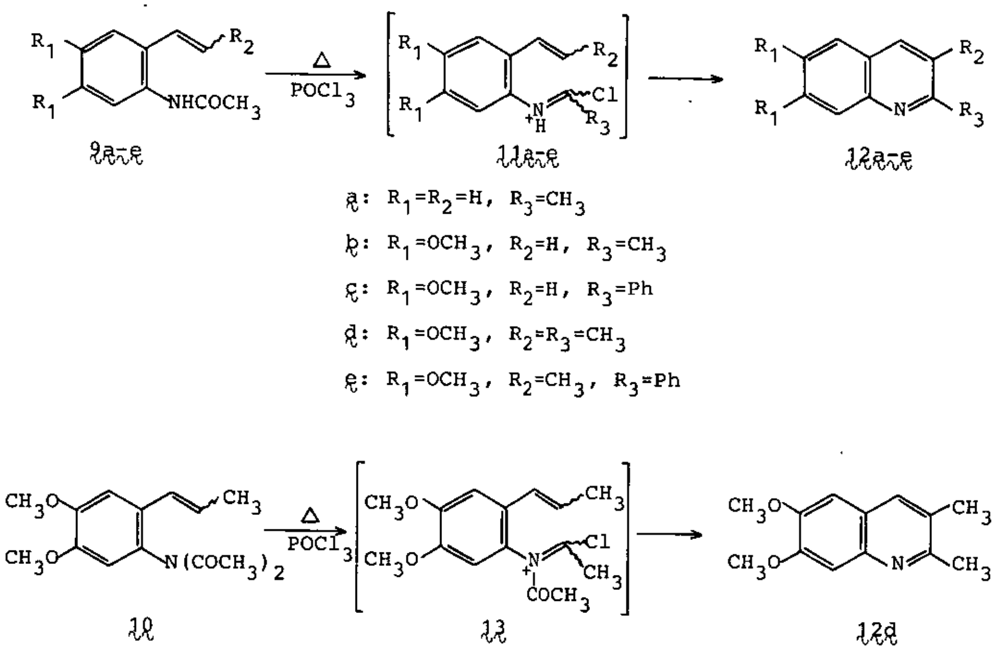


$6a$: R_1=H
$6b$: R_1=OCH_3
$7a$: R_1=R_2=H
$7b$: R_1=OCH_3, R_2=H
$7c$: R_1=OCH_3, R_2=CH_3
$8a$: R_1=R_2=H
$8b$: R_1=OCH_3, R_2=H
$8c$: R_1=OCH_3, R_2=CH_3
$9a$: R_1=R_2=H, R_3=CH_3
$9b$: R_2=OCH_3, R_2=H, R_3=CH_3
$9c$: R_1=OCH_3, R_2=H, R_3=Ph
$9d$: R_1=OCH_3, R_2=R_3=CH_3
$9e$: R_1=OCH_3, R_2=CH_3, R_3=Ph
8c
10

Scheme 2

system, we started from 2-nitrobenzaldehyde (6). Wittig reaction of 2-nitrobenzaldehyde (6a) or (6b) with methylenetriphenylphosphorane or ethylenetriphenylphosphorane gave 2-nitrostyrenes (7a), (7b) and (7c; a mixture of cis/trans) (89%, 90% and 94%), respectively. Subsequent reduction of nitro group of (7a), (7b) and (7c) with sodium hydrosulfite in aqueous methanol afforded anilines (8a), (8b) and (8c), respectively, which were immediately treated with acetyl chloride or benzoyl chloride in the presence of potassium carbonate to give 2-alkenyl acylanilines (9a-e) (40-71%) as shown in Scheme 2. N-Diacetyl compound (10) was prepared by acetylation of aniline (8c) with acetic anhydride and pyridine. Thermal cyclization of 2-alkenyl acylanilines (9a-e) with phosphorus oxychloride in toluene or xylene provided expected quinolines (12b-e) in good yield as shown in Scheme 3 and Table 1. The variation of yield by the difference of reaction temperature between toluene and xylene was not observed. In the case of unsubstituted anilide (9a), this thermal cyclization seems to be more difficult than substituted anilides having an electron donating group. In a similar way, N-diacetyl compound (10) was also treated with $POCl_3$ in both solvents under reflux to give quinoline (12d) in good yield.

Recently, Kametani and coworkers[1b,c] have reported the electrocyclic reaction of 2-azahexatriene system derived from the Schiff's base of 2-amino-α-methylstyrene with aldehydes provided quinoline derivatives in 12-43% yield (except one case). In contrast, our reaction seems to be an ionic reaction mechanism based on the effect of substituent rather than a kind of the electrocyclic reaction from a point



a: $R_1=R_2=H$, $R_3=CH_3$
b: $R_1=OCH_3$, $R_2=H$, $R_3=CH_3$
c: $R_1=OCH_3$, $R_2=H$, $R_3=Ph$
d: $R_1=OCH_3$, $R_2=R_3=CH_3$
e: $R_1=OCH_3$, $R_2=CH_3$, $R_3=Ph$

Scheme 3

Table 1

2-Alkenyl Acylaniline	Solvent	Products	Yield[a)] (%)
9a	Toluene	12a	34
9b	Toluene	12b	76
9b	Xylene	12b	82
9c	Toluene	12c	80
9c	Xylene	12c	82
9d	Toluene	12d	87
9d	Xylene	12d	80
9e	Toluene	12e	88
9e	Xylene	12e	90
10	Toluene	12d	88
10	Xylene	12d	87

a) isolated yield.

of the high yield. A reasonable mechanism for the formation of quinoline (12) may involve a three step sequence as follows. The initial step forms the iminium salt (11) or the N-acyliminium salt (13) that is 2-azahexatriene system. This is followed by intramolecular cyclization promoted with the methoxy group to form the dihydro compound. Finally, the aromatization proceeds smoothly along with an elimination of hydrogen chloride based on the effect of the methoxy group to give quinoline (12). Namely, this reaction suggests that the methoxy group will play an important part in this cyclization and subsequent elimination of chlorine atom for the aromatization. This reaction also demonstrates that both of the cyclization and the aromatization have not been restricted by the geometry of alkene and /or iminium salt.

Thus, we found that the thermal cyclization of 2-azahexatriene system generated from 2-alkenyl acylaniline with $POCl_3$ under the reflux condition of toluene or xylene is effective to the synthesis of substituted quinoline nucleus.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a Shimadzu IR-408 spectrophotometer. NMR spectra were taken with a JEOL PMX-60 spectrometer and mass spectra were recorded on a Shimadzu GC-MS 6020 mass spectrometer.

General Procedure for the Synthesis of 2-Nitrostyrene (7) —— A solution of n-BuLi (1.65 M solution in hexane, 51 mmol) was added to an ice-cooled solution of methyl triphenylphosphonium bromide or ethyl triphenylphosphonium bromide (51 mmol) in anhydrous THF (70 ml) under a N_2 stream. After completion of ylide formation (about 30 min), a solution of nitroaldehyde (6) (50 mmol) in anhydrous THF (100 ml) was added to the solution of ylide and the mixture was stirred at room temperature overnight. The mixture was worked up with brine, and extracted with $CHCl_3$ (150 ml X 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography (silica gel, 150 g) using benzene/hexane (1:1) to give nitrostyrene (7).

2-Nitrostyrene (7a): 89%, mp 11°C; bp 96°C/5 torr (Lit.[4] mp 11°C).

4,5-Dimethoxy-2-nitrostyrene (7b): 90%, mp 87-88°C (from EtOH) (Lit.[5] mp 87-88°C). ν_{max}^{KBr} cm^{-1}: 1570, 1330 (NO_2). ^1H-NMR ($CDCl_3$, δ): 3.87(3H, s), 3.92(3H, s), 5.37

(1H, d, J=9Hz), 5.53(1H, d, J=15Hz), 6.85(1H, s), 7.18(1H, dd, J=15 and 9Hz). MS: m/z 209(M^+). *Anal*. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.45; H, 5.32; N, 6.66.

4,5-Dimethoxy-2-(1-propenyl)nitrobenzene (7c): 94%, mp 118-119.5°C (from EtOH) as yellow needles. ν_{max}^{KBr} cm^{-1}: 1570, 1330 (NO_2). ^{1}H-NMR ($CDCl_3$, δ): 1.92(3H, dd, J=6 and 2Hz), 3.88(3H, s), 3.93(3H, s), 5.80-6.36(2H, m), 6.87(1H, s), 7.47(1H, s). MS: m/z 223(M^+). *Anal*. Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.28; H, 5.80; N, 6.35.

General Procedure for the Synthesis of 2-Alkenyl acylaniline (9) —— A solution of $Na_2S_2O_4$ (70 mmol) in H_2O (50 ml) was added to a solution of nitro compound (7) in MeOH (50 ml) at room temperature. After 30 min, the solvent was removed under reduced pressure. The residue was washed several times with $CHCl_3$ containing MeOH (5%) and filtered. The filtrate was dried over anhydrous Na_2SO_4 and concentrated to give crude aniline (8), which was used to the next reaction. A solution of excess acetyl chloride (20-30 mmol) or benzoyl chloride (15 mmol) in $CHCl_3$ (5-10 ml) was added to a solution of crude aniline (8) in $CHCl_3$ (15-20 ml) in the presence of K_2CO_3 (20-30 mmol). The solution was stirred at room temperature for 2 h, which was washed with dilute HCl, aqueous $KHCO_3$ (saturated and brine. The $CHCl_3$ solution was concentrated and the residue was purified by column chromatography (silica gel, 20-30 g) using benzene/$CHCl_3$ (1:1) to give anilide (9).

2-Vinylacetanilide (9a): 40%, mp 94-95°C (Lit.[6] 94.5°C).

4,5-Dimethoxy-2-vinylacetanilide (9b): 64%, mp 174-176°C (from EtOH). ν_{max}^{KBr} cm^{-1}: 1640 (amide). ^{1}H-NMR ($CDCl_3$, δ): 2.18(3H, s), 3.87(6H, s), 5.27(1H, d, J=10Hz), 5.53(1H, d, J=18Hz), 6.50-7.47(3H, m). MS: m/z 221(M^+). *Anal*. Calcd for $C_{12}H_{15}NO_4$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.20; H, 6.79; N, 6.43.

4,5-Dimethoxy-2-(1-propenyl)acetanilide (9c): 60%, mp 130-130.5°C (from $CHCl_3$/Et_2O). ν_{max}^{KBr} cm^{-1}: 1640 (amide). ^{1}H-NMR ($CDCl_3$, δ): 1.82(3H, d, J=6Hz), 2.17 (3H, s), 3.82(6H, s), 5.77-6.27(1H, m), 6.80(1H, s), 7.23(1H, s), 7.45-7.80(1H, m). 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, 66.30; H, 7.33; N, 5.90.

4,5-Dimethoxy-2-vinylbenzanilide (9d): 71%, mp 177-179°C (from benzene). ν_{max}^{KBr} cm^{-1}: 1640 (amide). ^{1}H-NMR ($CDCl_3$, δ): 2.83(6H, s), 6.64-6.87(2H, m), 7.13-7.83 (8H, m). MS: m/z 283(M^+). *Anal*. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.05; H, 6.15; N, 5.02.

4,5-Dimethoxy-2-(1-propenyl)benzanilide (9e): 65%, mp 174-176°C (from benzene). ν^{KBr}_{max} cm^{-1}: 1630 (amide). ^{1}H-NMR (CDCl$_3$, δ): 1.90(3H, d, J=6Hz), 3.87(6H, s), 5.97-6.32(2H, m), 6.82(1H, s), 7.40-7.90(6H, m). 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, 72.50; H, 6.51; N, 4.66.

4,5-Dimethoxy-2-(1-propenyl)-N,N-diacetylaniline (10) —— A solution of $Na_2S_2O_4$ (12.2 g, 70 mmol) in H_2O (50 ml) was added to a solution of nitrostyrene (7c) (2.23 g, 10 mmol) in MeOH (50 ml) at room temperature. After being stirred for 30 min, the solvent was removed under reduced pressure. The residue was washed *several times with CHCl$_3$ containing MeOH (5%) and filtered.* The filtrate was dried and concentrated to give the crude aniline (8c) (1.2 g). Then, a solution of 8c, Ac_2O (10 ml) andpyridine (10 ml) was refluxed overnight. Excess Ac_2O and pyridine were removed under reduced pressure. The residue was dissolved in EtOAc, which was washed with diluted HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 20 g) with benzene/CHCl$_3$ (1:1) to give diacetyl compound (10) (1.52 g, 55% from 7c), mp 114.5-115.5°C as colorless prisms (from Et$_2$O). ν^{KBr}_{max} cm^{-1}: 1700 (amide). ^{1}H-NMR (CDCl$_3$, δ): 2.80-2.98(3H, m), 2.25(6H, s), 3.82 (3H, s), 3.88£3H, s), 6.00-6.20(2H, m), 6.47(1H, s), 6.95(1H, s). MS: m/z 277(M$^+$). *Anal*. Calcd for $C_{15}H_{19}NO_4$: *C, 64.96; H, 6.91; N, 5.05. Found: C, 65.10; H, 6.99; N, 5.01.*

General Procedure for the Synthesis of Quinoline (12) —— A mixture of 2-alkenyl acylaniline (9) (10 mmol) and POCl$_3$ (1 ml) in toluene (5 ml) or xylene (5 ml) was refluxed for 3-4 h. After removal of solvent and excess POCl$_3$, the residue was basified with aqueous ammonia and then extracted with CHCl$_3$. The CHCl$_3$ layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using benzene/CHCl$_3$ (1:1) to give quinoline (12). The synthesis of quinoline (12d) was done by a similar method as described above. Yields were listed in Table 1.

2-Methylquinoline (12a) was identical with an authentic sample.

6,7-Dimethoxy-2-methylquinoline (12b): mp 103°C (Lit.[7] 103°C).

6,7-Dimethoxy-2-phenylquinoline (12c): mp 133-134°C (Lit.[7] 130.5°C).

6,7-Dimethoxy-2,3-dimethylquinoline (12d): mp 111-113°C (Lit.[7] 112°C).

6,7-Dimethoxy-3-methyl-2-phenylquinoline (12e): mp 151-152°C (from Et$_2$O). ^{1}H-NMR (CDCl$_3$, δ): 2.40(3H, s), 2.97(6H, s), 6.93-7.77(8H, m). MS: m/z 279(M$^+$). *Anal*.

Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.28; H, 7.25; N, 5.13.

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This paper is dedicated to Prof. Tetsuji Kametani, President of Hoshi University (Emeritus Prof. of Tohoku University) on the occasion of his 70th birthday.

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