RING TRANSFORMATION OF CINNOLINES WITH YNAMINES[1]

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Abstract - Cinnolines having electron-withdrawing substituents at 4-position reacted with ynamines to give naphthalene derivatives and/or quinoline derivatives through [4+2] cycloaddition followed by elimination of nitrogen or hydrogen cyanide.

It is known that electron-deficient heteroaromatic systems easily undergo inverse-electron demanded Diels-Alder reactions,[2-3] so that these properties were widely applied to synthesis of natural products.[4-7]

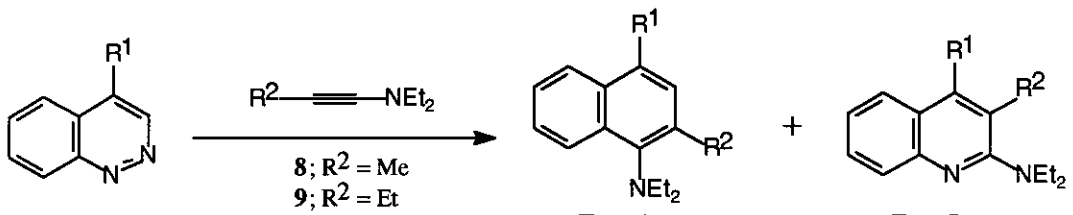
It has been reported by us that condensed pyridazines having electron-withdrawing group such as 1-phthalazinecarbonitrile reacted with ynamines, which are electron-rich dienophiles, to give naphthalene derivatives through [4+2] cycloaddition followed by elimination of nitrogen.[8]

In the research of our study,[8-10] we examined the scope and the limitation of the reaction of ynamines with cinnoline, that is fundamental part of fused pyridazine as well as phthalazine.

We examined reactivities of cinnolines having several substituents at 4-position with ynamines (Scheme 1). Cinnolines having electron-withdrawing group, such as cyano group, reacted smoothly with ynamines to give naphthalene derivatives with releasing nitrogen and/or quinoline derivatives with releasing hydrogen cyanide. In contrast, cinnolines with electron-donating group such as methyl group failed into recovery of starting materials.

4-Cinnolinecarbonitrile (**1**)[11] with ynamine (**8**) gave 4-diethylamino-3-methyl-1-naphthalenecarbonitrile and 2-diethylamino-3-methyl-4-quinolinecarbonitrile simultaniously. According to the molecular orbital theory, it is considered that the 1st LUMO and the 2nd LUMO[12] of **1** were participated in this reaction. The overlap between the 1st LUMO of **1** and the HOMO of ynamine gave quinoline derivatives and the naphthalene derivatives were made from the overlap between the 2nd LUMO of **1** and the ynamine's HOMO. On the other hand, in the reaction of ethyl cinnnoline-4-carboxylate (**2**) with ynamines only naphthalene derivatives were detected. This is due to the steric hindrance of ester group. So the overlap between the 2nd LUMO of **2** and the HOMO of ynamine occures preferentially, and the 3-, 8a-adduct is obtained. The same results were observed in the reaction of 4-acetylcinnoline (**3**)[13] and 4-benzoylcinnoline (**4**)[11] with ynamines.

In the case of 4(1*H*)-cinnoline (**5**), ynamines reacted at the position of 4- and 1- of cinnoline ring and gave

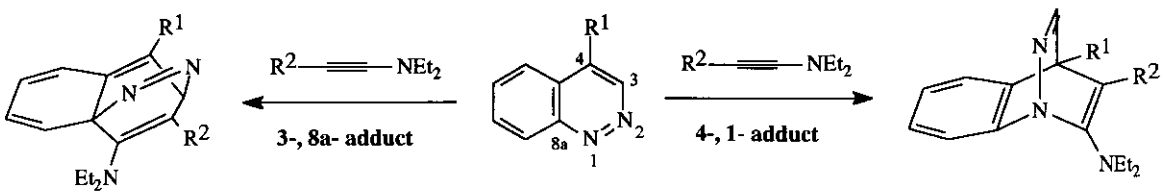


	R^1	R^2	Type A (de-nitrogen)	Type B (de-hydrogen cyanide)
1	CN	Me	44.9	30.7
1	CN	Et	51.2	22.3
2	CO_2Et	Me	51.4	–
2	CO_2Et	Et	64.7	–
3	COMe	Me	44.6	–
3	COMe	Et	43.2	–
4	COPh	Me	43.2	–
5	H	Me	–	58.1
5	H	Et	–	51.5
6	Me	Me	–	–
7	OMe	Me	–	–

Scheme 1

quinoline derivatives with releasing hydrogen cyanide. Cinnolines having electro-donating group at 4-position such as 4-methylcinnoline (**6**) or 4-methoxycinnoline (**7**) did not react with ynamine.

In conclusion, two directions of cycloaddition were obseved in the reaction of 4-substituted cinnnolines with electron-rich ynamines. In the reaction, the overlap between the 1st LUMO of cinnoline and the HOMO of ynamine gave the quinoline derivatives *via* 4-,1- adduct at cinnoline, and the naphthalene derivatives were made from the overlap between the 2nd LUMO of cinnoline and the ynamine's HOMO *via* 3-, 8a- adduct (Scheme 2). In addition, in the case of the steric hindrance at the 4-position, the 2nd LUMO of cinnoline preferentially participates in the cycloaddition at the 3- and 8a- position of cinnnoline.



Scheme 2

EXPERIMENTAL

All melting points are uncorrected. Infrared absorption spectra were recorded on a Jasco A-102 diffraction grating ir spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were measured at 270 MHz on a JEOL instrument. Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-nmr signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Mass spectra were recorded with a JEOL JMS D-100 mass spectrometer. Column chromatgraphy was carried out on silica gel (Merck Co. Ltd., 200 mesh).

Reaction of 4-Cinnolinecarbonitrile (1) with Ynamines

Compound (**1**) (300 mg, 1.9 mmol) in 2 ml of dry dioxane was added to *N,N*-diethyl-1-propynylamine (**8**) (537 mg, 5.7 mmol) and the solution was refluxed for 2 h under Ar atmosphere. After being cooled, the reaction mixture was quenched with water and acetic acid, and extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel). The first fraction eluted with hexane/benzene=5/1 gave 4-diethylamino-3-methyl-1-naphthonitrile, mp 108 -110°C (picrate, from methanol) in 44.9% (207 mg) yield. Ms m/z: 238 (M^+). Ir (neat): 2214cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.29 - 8.14 (2H, m), 7.73 (1H, s), 7.60 - 7.53 (2H, m), 3.33 (4H, q, *J*=7.0 Hz), 2.45 (3H, s), 1.05 (6H, t, *J*=7.0 Hz). ^{13}C-Nmr ($CDCl_3$): 150.3, 136.6, 133.8, 133.6, 132.7, 127.2, 126.8, 125.8, 125.4, 118.3, 106.4, 47.8, 19.4, 14.6. *Anal.* Calcd for $C_{16}H_{18}N_2 \cdot C_6H_3N_3O_7$ (picrate): C, 56.53; H, 4.53; N, 14.98. Found: C, 56.49; H, 4.40; N, 15.19. The second fraction eluted with hexane/benzene=2/3 gave 2-diethylamino-3-methyl-4-quinolinecarbonitrile, mp 148 - 150°C (picrate, from methanol) in 30.7% (142 mg) yield. Ms m/z: 239 (M^+). Ir (neat): 2218cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.06 (1H, d, *J*=8.5 Hz), 8.02 (1H, d, *J*=8.5 Hz), 7.70-7.61 (2H, m), 3.44 (4H, q, *J*=7.1 Hz), 2.73 (3H, s), 1.14 (6H, t, *J*=7.1 Hz). ^{13}C-Nmr ($CDCl_3$): 160.7, 147.3, 143.4, 133.8, 129.1, 129.0, 128.0, 126.1, 123.9, 115.9, 113.5, 46.9, 22.7, 13.6. *Anal.* Calcd for $C_{15}H_{17}N_3 \cdot C_6H_3N_3O_7$ (picrate): C, 53.85; H, 4.30; N, 17.94. Found: C, 53.88; H, 4.11; N, 18.04.

By the reaction of **1** with *N,N*-diethyl-1-butynylamine (**9**), 4-diethylamino-3 ethyl-1-naphthonitrile was obtained, mp 106 - 108°C (picrate, from methanol), in 51.2% yield from the first fraction eluted with hexane/benzene=5/1. Ms m/z: 252 (M^+). Ir (neat): 2216cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.28 - 8.24 (1H, m), 8.19 (1H, m), 7.82 (1H, s), 7.61 - 7.52 (2H, m), 3.32 (4H, q, *J*= 7.0Hz), 2.87 (2H, q, *J*=7.5 Hz), 1.30 (3H, t, *J*=7.5 Hz), 1.06 (6H, t, *J*=7.0 Hz). ^{13}C-Nmr ($CDCl_3$): 149.9, 140.4, 134.8, 134.1, 132.5, 127.3, 126.8, 125.9, 125.4, 118.4,

107.2, 48.7, 24.4, 15.0, 14.8. *Anal.* Calcd for $C_{17}H_{20}N_2 \cdot C_6H_3N_3O_7$ (picrate): C, 57.38; H, 4.81; N, 14.55. Found: C, 57.40; H, 4.72; N, 14.72. The second fraction eluted with hexane/benzene=2/3 gave 2-diethylamino-3-ethyl-4 quinolinecarbonitrile, mp 144 - 147°C (picrate, from methanol), in 22.3% (109 mg) yield. Ms m/z: 253 (M^+). Ir (neat): 2216cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.07 - 8.04 (2H, m), 7.72 - 7.58 (2H, m), 3.43 (4H, q, *J*=7.1 Hz), 3.04 (2H, q, *J*=7.5 Hz), 1.40 (3H, t, *J*=7.5 Hz), 1.15 (6H, t, *J*=7.1 Hz). ^{13}C-Nmr ($CDCl_3$): 165.2, 147.0, 144.2, 129.2, 129.0, 127.9, 125.9, 123.9, 116.0, 113.9, 47.3, 27.4, 13.5, 13.1. *Anal.* Calcd for $C_{15}H_{17}N_3 \cdot C_6H_3N_3O_7$ (picrate): C, 53.85; H, 4.30; N, 17.94. Found: C, 53.88; H, 4.11; N, 18.04.

Reaction of Ethyl Cinnoline-4-carboxylate (2) with Ynamines

Compound (**2**) (300 mg, 1.5 mmol) in 2 ml of dry dioxane was added **8** (490 mg, 4.4 mmol) and the solution was refluxed for 2 h under Ar atmosphere. After being cooled, the reaction mixture was quenched with water and acetic acid, and extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel). The fraction eluted with hexane gave ethyl 4-diethylamino-3-methyl-1-naphthoate as pale yellow oil in 51.4% (218 mg) yield. Ms m/z: 285 (M^+). Ir (neat): 1651cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.87 - 8.84 (1H, m), 8.32 - 8.28 (1H, m), 8.01 (1H, s), 7.53 - 7.46 (2H, m), 4.45 (2H, q, *J*=7.0 Hz), 3.31 (4H, q, *J*=7.0 Hz), 2.47 (3H, s), 1.45 (3H, t, *J*=7.0 Hz), 1.31 (6H, t, *J*=7.0 Hz). ^{13}C-Nmr ($CDCl_3$): 167.7, 149.4, 134.3, 132.8, 131.5, 128.8, 126.4, 125.9, 125.6, 125.4, 124.1, 60.9, 47.9, 19.6, 14.6, 14.5.

By the reaction of **2** with **9**, ethyl 4-diethylamino-3-ethyl-1-naphthoate was obtained as pale yellow oil in 64.7% yield from the fraction eluted with hexane. ^{1}H-Nmr ($CDCl_3$): 8.86 - 8.83 (1H, m), 8.30 - 8.27 (1H, m), 8.07 (1H, s), 7.54 - 7.45 (2H, m), 4.47 (2H, q, *J*=7.0 Hz), 3.31 (4H, q, *J*=7.0 Hz), 2.88 (2H, q, *J*=7.0 Hz), 1.46 (3H, t, *J*=7.0 Hz), 1.31 (3H, t, *J*=7.0 Hz), 1.04 (6H, t, *J*=7.0 Hz). ^{13}C-Nmr ($CDCl_3$): 167.8, 148.9, 139.6, 134.7, 132.7, 132.4, 131.3, 126.4, 125.9, 125.6, 124.9, 60.9, 48.8, 24.7, 15.3, 14.8, 14.5.

Reaction of 4-Acetylcinnoline (3) and 4-Benzoylcinnoline (4) with Ynamines

Compound (**3**) (300 mg, 1.7 mmol) in 2 ml of dry dioxane was added to **8** (581 mg, 3.8 mmol) and the solution was refluxed for 2 h under Ar atmosphere. After being cooled, the reaction mixture was quenched with water and acetic acid, and extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel). The fraction eluted with hexane/ethyl acetate=4/1 gave 1-acetyl-4-diethylamino-3-methylnaphthalene as pale yellow oil in 44.6% (193 mg) yield. Ms m/z: 255 (M^+). Ir (neat): 1670cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.75 - 8.71 (1H, m), 8.30 - 8.26 (1H, m), 7.77 (1H, s), 7.53 - 7.45 (2H, m), 3.33 (4H, q, *J*=7.1 Hz), 2.73 (3H, s), 2.49 (3H, s), 1.05 (6H, t, *J*=7.1 Hz). ^{13}C-Nmr ($CDCl_3$): 201.7, 149.5, 134.5, 133.5, 132.3, 132.2, 130.5, 126.8, 126.2, 125.8, 125.3, 47.9, 29.9, 19.7, 14.6.

By the reaction of **3** with **9**, 1-acetyl-4-diethylamino-3 ethylnaphthalene was obtained as pale yellow oil in 43.2% yield from the fraction eluted with hexane/ethyl acetate=4/1. Ms m/z: 269 (M^+). Ir (neat): 1670cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.72 - 8.68 (1H, m), 8.28 - 8.24 (1H, m), 7.83 (1H, s), 7.53 - 7.45 (2H, m), 3.31 (4H, q, *J*=7.1Hz), 2.89 (2H, q, *J*=7.6 Hz), 2.73 (3H, s), 1.31 (3H, t, *J*=7.6 Hz), 1.06 (6H, t, *J*=7.1 Hz). ^{13}C-Nmr ($CDCl_3$): 201.7, 148.9, 139.2, 134.7, 133.1, 131.3, 130.3, 126.8, 126.2, 125.8, 125.5, 48.8, 30.0, 24.7, 15.3, 14.9.

By the reaction of **4** with **8**, 1-benzoyl-4 diethylamino-3-methylnaphthalene was obtained as pale yellow oil in 43.2% yield from the fraction eluted with hexane/ethyl acetate=5/1. Ir (neat): 1651cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 8.34 - 8.31 (1H, m), 8.08 - 8.05 (1H, m), 7.53-7.45 (8H, m), 3.35 (4H, q, *J*=6.9 Hz), 2.45 (3H, s), 1.09 (6H, t, *J*=6.9 Hz). ^{13}C Nmr ($CDCl_3$): 198.1, 148.0, 138.8, 134.5, 132.7, 132.6, 132.4, 131.3, 130.4, 128.4, 126.4, 126.0, 125.9, 125.8, 125.4, 123.3, 48.0, 19.6, 14.8.

Reaction of 4(1*H*)-Cinnoline (5) with Ynamines

Compound (**5**) (300 mg, 2.3 mmol) in 2 ml of dry dioxane was added to **8** (769 mg, 6.9 mmol) and the solution was refluxed for 2 h under Ar atmosphere. After being cooled, the reaction mixture was quenched with water and acetic acid, and extracted with chloroform. The organic layer was washed with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel). The fraction eluted with hexane/ethyl acetate=4/1 gave 2-diethylamino-3-methylquinoline, mp 144-146 (picrate, from methanol), in 58.1% (287mg) yield. Ms m/z: 214 (M^+). ^{1}H-Nmr ($CDCl_3$): 7.82 - 7.79 (1H, m), 7.73 (1H, s), 7.59-7.47 (2H, m), 7.30 - 7.24 (1H, s), 3.36 (4H, q, *J*=7.0 Hz), 2.40 (3H, s), 1.17 (6H, t, *J*=7.0 Hz). ^{13}C-Nmr ($CDCl_3$): 160.8, 146.0, 137.8, 128.1, 127.3, 126.3, 125.9, 125.3, 123.5, 44.8, 19.7, 13.4.

By the reaction of **5** with **9**, 2-diethylamino-3-ethylquinoline was obtained, mp 140-143 (picrate, from methanol), in 51.5% yield from the fraction eluted with hexane/ethyl acetate=4/1. Ms m/z: 228 (M^+). ^{1}H-Nmr ($CDCl_3$): 7.85 - 7.82 (1H, m), 7.80 (1H, s), 7.64 - 7.49 (2H, m), 7.33 - 7.27 (1H, s), 3.32 (4H, q, *J*=7.1 Hz), 2.76 (2H, q, *J*=7.4 Hz), 1.31 (3H, t, *J*=7.4 Hz), 1.15 (6H, t, *J*=7.1 Hz). ^{13}C-Nmr ($CDCl_3$): 160.8, 145.7, 135.6, 132.6, 128.1, 127.4, 126.5, 125.6, 123.8, 45.4, 24.6, 14.1, 13.3. Anal. Calcd for $C_{15}H_{20}N_2 \cdot C_6H_3N_3O_7$ (picrate): C, 55.14; H, 5.07; N, 15.31. Found: C, 55.10; H, 5.05; N, 15.37.

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