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Cycloadditions in Syntheses. XXIV.[1] 1,2-Dihydrocyclobut[*c*]isoquinoline

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1,2-Dihydrocyclobut[*c*]isoquinoline was synthesized through photochemical 2+2 cycloaddition of 3-methoxyisoquinolin-1(2*H*)-one to 1,1-dichloroethylene.

Keywords——1,2-dihydrocyclobut[*c*]isoquinoline; photochemical 2+2 cycloaddition; photochemical synthesis; 1,2-dihydrocyclobut[*c*]isoquinoline 4-substituted; zinc reduction; 1,1-dichloroethylene

Previously, we reported the synthesis of 1,2-dihydrocyclobuta[*c*]quinoline, a new aza-analogue of naphthocyclobutene at that time, through 1,2-dihydrocyclobuta[*c*]quinolin-3(4*H*)-one obtained by photocycloaddition of 4-methoxy-2-quinolone to ethylene, followed by elimination of methanol from the adduct.[3] Later, this procedure was successfully applied to the synthesis of 1,2-dihydrocyclobuta[*c*]pyridine.[4] Several 1-substituted 1,2-dihydrocyclobut[*c*]isoquinolin-4(3*H*)-ones were also synthesized from 3-methoxy-1-isoquinolone essentially by the same two-step procedure using an appropriate alkene in the first photoaddition step.[5]

As a result, a general and simple synthetic method (Kaneko–Naito method[6]) for cyclobutene-fused heteroaromatics has been established, which consists of i) photochemical 2+2 cycloaddition of heteroaromatics containing a β-alkoxyenone or δ-alkoxydienone function in the ring system to alkenes, and ii) elimination of the alcohol from the adducts. In this method, the alkoxy group acts as a leaving group in the second step and can be replaced with other groups such as chlorine. The method was successfully applied to cyclobutene annelation to the other heteroaromatics such as thiocoumarin,[7] uracil,[8] and very recently, even to naphthoquinone derivatives.[9]

It is sometimes difficult, however, to achieve an efficient photoaddition if we use ethylene itself as the alkene in the photoaddition step, because ethylene not only exhibits low solubility in ordinary organic solvents but also has relatively low reactivity in photoaddition reactions.[10]

In order to overcome these difficulties, we have now developed a modified procedure to synthesize an unsubstituted cyclobutene-fused heteroaromatic compound using 1,1-dichloroethylene instead of ethylene and demonstrated its usefulness for the synthesis of 1,2-dihydrocyclobut[*c*]isoquinoline, a so-far unknown aza-analogue of naphthocyclobutene.

Though the photoaddition of 3-methoxyisoquinolin-1(2*H*)-one (**1**) to electron-deficient alkenes proceeded smoothly, the same addition did not proceed efficiently to ethylene or to an electron-rich alkene, unless a large excess of the latter was present in the irradiated solution.[5,6] It seems noteworthy that upon irradiation ($\geq$300 nm), **1** is more unstable than 4-methoxyquinolin-2(1*H*)-one, and hence longer irradiation results in the decomposition of **1**.[11]

In order to effect a more efficient photoaddition, we irradiated **1** in acetonitrile in the presence of a large excess of 1,1-dichloroethylene (bp 30—32 °C), which is not only freely soluble in ordinary organic solvents but also is somewhat more electron-deficient than ethylene. As a result, the expected 2+2 photoadducts were obtained as a mixture of two regioisomers (**2** and **3**) which could be separated easily by column chromatography in yields of 78% and 2%, respectively. The regiochemistries of compounds **2** and **3** were elucidated by comparison of their nuclear magnetic resonance (NMR) spectra. Specifically, in the spectrum of the minor adduct (**3**) a signal due to the methine proton (C_{8b}-H) is observed at δ 3.81 as the X part of an ABX system with $J_{AX} = 10$ and $J_{BX} = 8.5$ Hz, further split by coupling ($J = 1.5$ Hz) with the NH proton, whereas that of the major adduct (**2**) is observed at δ 4.34 as a broad singlet. It is clear that the major adduct is the 1,1-dichloro compound (**2**), while the minor one is the 2,2-dichloro compound (**3**).[12] Heating of the major adduct (**2**) with phosphorus oxychloride then afforded 1,1,4-trichloro-1,2-dihydrocyclobut[*c*]isoquinoline (**4**) in 72% yield. This step proceeds by elimination of methanol[13] followed by chlorination at the 4-position.

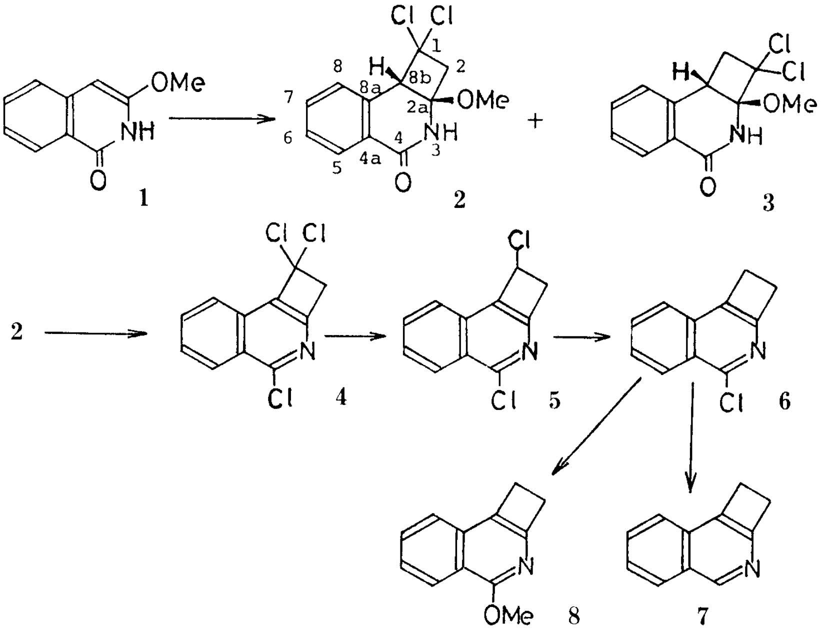

Chart 1

Previously, using zinc dust in an acidic medium, 3-chloro-1,2-dihydrocyclobuta[*c*]quinoline was successfully reduced to 1,2-dihydrocyclobuta[*c*]quinoline.[3,4] Based on this fact, reduction of **4** using this reagent has been examined.[14,15] Thus, refluxing of **4** in ethanol in the presence of zinc was found to give 4-chloro-1,2-dihydrocyclobut[*c*]isoquinoline (**6**) in 74% yield. If the reduction was terminated at the point when almost all of the starting material (**4**) was consumed [the reaction can be followed by thin layer chromatography (TLC)], 1,4-dichloro-1,2-dihydrocyclobut[*c*]isoquinoline (**5**) was obtained. Even if the reduction of **4** was carried out for a further long period, the desired product [1,2-dihydrocyclobut[*c*]isoquinoline (**7**)] was not formed. These results indicate that zinc in ethanol only reduces the chlorine atoms at the 1-position and not the one at the 4-position in **4**. The chlorine atom in **6**, however, can be replaced with a suitable nucleophile just as in ordinary 1-haloisoquinolines, as demonstrated in the following experiment. Thus, treatment of **6** with sodium methoxide in methanol gave the corresponding 4-methoxy compound (**8**) in a quantitative yield.

Since zinc in a neutral medium could not effect the reductive removal of the chlorine atom in **6**, as mentioned above, we then employed this reagent in an acidic medium. Thus, refluxing (1.5 h) of **6** in a mixture of acetic acid and *tert*-butanol in the presence of zinc gave 1,2-dihydrocyclobut[*c*]isoquinoline (**7**) in nearly quantitative yield. It seems noteworthy that direct reduction of the trichloro compound (**4**) under the above conditions only afforded the desired cyclobutaisoquinoline (**7**) in a low yield (*ca.* 10%) and the reduction terminated mostly at the stage of the 4-chloro compound to give **6** as the major product.

In summary, we have successfully applied our photochemical procedure (Kaneko–Naito method) for the synthesis of cyclobutene-fused heteroaromatics to the isoquinoline series and have achieved the first synthesis of 1,2-dihydrocyclobut[*c*]isoquinoline (**7**). At the same time, 1,1-dichloroethylene was found to be an alternative reagent to ethylene itself in the photoaddition step of the Kaneko–Naito method.

Experimental

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 spectrometer and ultraviolet (UV) spectra with a Hitachi 320 spectrometer. Except for **7** (the key compound in the present work), UV spectra of **2**—**6** and **8** were measured at appropriate concentrations and hence, only the wavelengths of their maxima are recorded. ^{1}H-NMR spectra were taken on a JEOL JNM-60 or JEOL JNM-FX-100 spectrometer (with tetramethylsilane as an internal standard) and chemical shifts are expressed in δ values. Mass spectra (MS) were taken with a Hitachi M-80 spectrometer.

Column chromatography was carried out on silica gel (100—200 mesh) purchased from Kanto Chemical Co., Inc. and TLC on a Chromatotron (Harrison Research, model 7924; centrifugally accelerated, radial TLC apparatus for preparative purposes) using Merck Silica gel GF_{254} (type 60).

Photochemical Cycloaddition of 3-Methoxyisoquinolin-1(2*H*)-one (1) to 1,1-Dichloroethylene——A solution of **1** (823.5 mg) in a mixture of 1,1-dichloroethylene (50 ml) and acetonitrile (370 ml) was irradiated through a Pyrex filter with an Ushio 450 W high-pressure mercury lamp for 45 min under an argon atmosphere. After filtration to remove some precipitate, the reaction mixture was concentrated *in vacuo* and chromatographed on silica gel (30 g). A fraction eluted with 2% MeOH–CH_2Cl_2 was recrystallized to give 903.1 mg of **2**. The mother liquor was separared on the Chromatotron (2% MeOH–CH_2Cl_2) to give 27.3 mg (2%) of **3** and 90.7 mg of **2**. The combined yield of **2** was 993.8 mg (78%).

1,1-Dichloro-2a-methoxy-1,2,2a,8b-tetrahydrocyclobut[*c*]isoquinolin-4(3*H*)-one (**2**): mp 133—134 °C (AcOEt), colorless prisms. UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 232.5, 277, 288. IR (KBr): 1662 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.09 (s, 3H), 3.23 (d, J= 13.5 Hz, 1H), 3.50 (dd, J= 13.5, 0.8 Hz, 1H), 4.34 (br s, 1H), 6.90—7.60 (m, 4H), 8.00—8.25 (m, 1H). *Anal.* Calcd for $C_{12}H_{11}Cl_2NO_2$: C, 52.96; H, 4.07; N, 5.15. Found: C, 52.89; H, 3.98; N, 4.96.

2,2-Dichloro-2a-methoxy-1,2,2a,8b-tetrahydrocyclobut[*c*]isoquinolin-4-(3*H*)-one (**3**): mp 191—192 °C (AcOEt–Et_2O), colorless prisms. UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 234, 278, 288. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (dd, J= 11.8, 10.0 Hz, 1H), 3.10 (dd, J= 11.8, 8.5 Hz, 1H), 3.28 (s, 3H), 3.81 (ddd, J= 10.0, 8.5, 1.5 Hz, 1H), 6.50 (br s, 1H), 7.00—7.60 (m, 3H), 8.00—8.25 (m, 1H). *Anal.* Calcd for $C_{12}H_{11}Cl_2NO_2$: C, 52.96; H, 4.07; N, 5.15. Found: C, 52.80; H, 4.15; N, 4.86.

1,1,4-Trichloro-1,2-dihydrocyclobut[*c*]isoquinoline (4)——A solution of **2** (508.8 mg) in 20 ml of $POCl_3$ was refluxed for 1.5 h. After evaporation of excess $POCl_3$ *in vacuo*, ice-water was added and the solution was basified by adding aq. $NaHCO_3$. The product was extracted with CH_2Cl_2 and the organic layer was washed with water and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was chromatographed on the Chromatotron (CH_2Cl_2) to give 346.0 mg (72%) of **4** as colorless prisms, mp 146—146.5 °C (hexane–ether). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 225.5, 267 sh, 277, 290 sh, 330, 338. IR (KBr): 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.27 (s, 2H), 7.40—7.95 (m, 3H), 8.20—8.45 (m, 1H). *Anal.* Calcd for $C_{11}H_6Cl_3N$: C, 51.10; H, 2.34; N, 5.42. Found: C, 51.26; H, 2.06; N, 5.53.

4-Chloro-1,2-dihydrocyclobut[*c*]isoquinoline (6)——Zinc dust (600 mg) was added to a solution of **4** (262.4 mg) in 20 ml of 99% EtOH, and the whole was reluxed for 10 h. The precipitate was removed by filtration, the filtrate was evaporated *in vacuo*, the residue was made basic with aq. $NaHCO_3$, and the whole was extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated, then the residue was separated on the Chrômatotron (2% MeOH–CH_2Cl_2) to give 142.9 mg (74%) of **6** as colorless prisms, mp 86—87 °C (hexane–ether). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 221, 264 sh, 277, 289, 331, 340. IR (KBr): 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (an A_2B_2 pattern, 4H), 7.25—7.70 (m, 3H), 8.10—8.40 (m, 1H). *Anal.* Calcd for $C_{11}H_8ClN$: C, 69.67; H, 4.25; N, 7.39. Found: C, 69.52; H, 4.07; N, 7.30. MS m/z: 191, 189 (M^+).

1,4-Dichloro-1,2-dihydrocyclobut[*c*]isoquinoline (5)——A solution of **4** (77.8 mg) in 6 ml of 99% EtOH was refluxed for 4 h in the presence of zinc dust (100 mg). Treatment of the reaction products as above gave 24.6 mg (43%) of **6** and 21.4 mg (32%) of **5** as colorless prisms, mp 82—83 °C (hexane–ether). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 224, 266 sh, 277, 289, 330, 343 sh. IR (KBr): 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (dd, J= 14.0, 2.2 Hz, 1H), 4.08 (dd, J= 14.0, 3.8 Hz, 1H), 5.44 (dd, J= 3.8, 2.2 Hz, 1H), 7.40—7.90 (m, 3H), 8.20—8.50 (m, 1H). High-resolution MS m/z: M^+ Calcd for

$C_{11}H_7Cl_2N$: 222.9955 (2 × ^{35}Cl), 224.9926 ($^{35}Cl+^{37}Cl$), 226.9896 (2 × ^{37}Cl). Found: 222.9969, 224.9902, 226.9913.

4-Methoxy-1,2-dihydrocyclobut[*c*]isoquinoline (8)——Compound **6** (50.0 mg) was added to a solution of NaOMe in MeOH prepared from 20 mg of Na and 2 ml of ab. MeOH, and the reaction mixture was refluxed for 7 h. After removal of the solvent, the residue was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was separated on the Chromatotron (2% MeOH–CH_2Cl_2) to give 44.8 mg (92%) of **8** as colorless prisms, mp 35—36 °C (hexane). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 204, 279, 289, 332, 345 sh. IR (KBr): 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (an A_2B_2 pattern, 4H), 4.04 (s, 3H), 7.15—7.70 (m, 3H), 8.05—8.30 (m, 1H). High-resolution MS *m*/*z*: M$^+$ Calcd for $C_{12}H_{11}NO$: 185.0840. Found: 185.0828.

1,2-Dihydrocylobut[*c*]isoquinoline (7)——Zinc dust (400 mg) was added to a solution of **6** (103.0 mg) in 6 ml of 2.5% AcOH–*tert*-BuOH and the mixture was refluxed for 30 min. Further amounts of zinc dust (200 mg) and 2.5% AcOH–*tert*-BuOH (1 ml) were added to the reaction mixture and the whole was again refluxed for 1 h. After addition of CH_2Cl_2 and then aq. $NaHCO_3$ to basify the aqueous layer, followed by filtration, the organic layer was washed with water and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was separated on the Chromatotron (5% MeOH–CH_2Cl_2) to give 82.5 mg (98%) of **7** as colorless prisms, mp 57.5—58.5 °C (hexane). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm (log ε): 219.5 (4.81), 263 (3.49), 272.5 (3.49), 285 sh (3.28), 325 (3.65), 334 (3.66), 338.5 (3.65). UV $\lambda_{\max}^{\mathrm{HCl-MeOH}}$ nm (log ε): 228.5 (4.72), 267 (3.36), 277 (3.35), 290 sh (2.96), 342 sh (3.82), 351.5 (3.84). IR (KBr): 1628 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.10—3.35 (m, 2H), 3.35—3.60 (m, 2H), 7.20—7.70 (m, 3H), 7.75—8.00 (m, 1H), 8.94 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 25.58 (t), 33.92 (t), 121.34 (d), 125.63 (d), 129.04 (s), 129.57 (d), 130.69 (d), 132.16 (s), 132.79 (s), 152.87 (d), 155.94 (s). High-resolution MS *m*/*z*: M$^+$ Calcd for $C_{11}H_9N$: 155.0733. Found: 155.0706. *Anal.* Calcd for $C_{11}H_9N$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.39; H, 5.74; N, 9.19. Picrate of **7**: mp 215—217 °C, (dec.) (MeOH), yellow prisms. *Anal.* Calcd for $C_{17}H_{12}N_4O_7$: C, 53.13; H, 3.15; N, 14.58. Found: C, 53.23; H, 2.94; N, 14.45.

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References and Notes

1) Part XXIII: C. Kaneko, N. Katagiri, K. Uchiyama, and T. Yamada, *Chem. Pharm. Bull.*, **33**, 4160 (1985).
2) Present address: *Eisai Co., Ltd., Tokodai 5-Chome, Toyosato-machi, Tsukuba-gun, Ibaraki 300–26, Japan.*
3) C. Kaneko, T. Naito, and N. Nakayama, *Chem. Pharm. Bull.*, **29**, 593 (1981).
4) C. Kaneko, T. Naito, Y. Momose, H. Fujii, N. Nakayama, and I. Koizumi, *Chem. Pharm. Bull.*, **30**, 519 (1982).
5) T. Naito and C. Kaneko, *Tetrahedron Lett.*, **22**, 2671 (1981).
6) Reviews on this topic: *a*) C. Kaneko and T. Naito, *Heterocycles*, **19**, 2183 (1982); *b*) T. Naito and C. Kaneko, *Yuki Gosei Kagaku Kyokai Shi*, **42**, 51 (1984).
7) C. Kaneko, T. Naito, and T. Ohashi, *Heterocycles*, **20**, 1275 (1983).
8) C. Kaneko and N. Shimomura, *Tetrahedron Lett.*, **23**, 2571 (1982).
9) T. Naito, Y. Makita, and C. Kaneko, *Chem. Lett.*, **1984**, 921.
10) In these photoaddition reactions, electron-rich olefins add more efficiently to 2-quinolones than electron-deficient ones, while the reverse electron demand exists in their addition to 1-isoquinolones.
11) 3-Methoxy-1-isoquinolone (**1**) is unstable on irradiation at ≥300 nm and slowly decomposed in the absence of suitable olefins. For example, **1** was hydrolyzed slowly to homophthalimide under irradiation (≥300 nm) in dichloromethane. This photo-catalyzed hydrolysis probably occurs because of a trace of water present in the solvent. Similar photo-instability was also observed for 3-chloro-1-isoquinolone: C. Kaneko, T. Naito, and C. Miwa, *Heterocycles*, **19**, 2275 (1982); See also, *idem, Chem. Pharm. Bull.*, **30**, 752 (1982).
12) Upon irradiation in the presence of 1,1-dichloroethylene, 1-isoquinolone itself afforded the corresponding 2+2 photoadducts as a 4 : 1 mixture of regioisomers, where the major isomer was the **2**-type adduct: G. R. Evanega and D. L. Fabiny, *Tetrahedron Lett.*, **1971**, 1749.
13) Elimination of an alcohol from the photoadducts obtained from heteroaromatics-containing a β-alkoxyenone or δ-alkoxydienone function in the ring system can be effected either by base or acid: see, references cited in 6*a*).
14) Since cyclobutene-fused heteroaromatics are known to be easily reduced under catalytic hydrogenation conditions,[3,4,15] this method can not be applied to remove chlorine atoms from **4**.
15) R. P. Thummel and D. K. Kohli, *J. Org. Chem.*, **43**, 4882 (1978); D. J. Haywood, C. J. Potter, and S. T. Reid, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2458.