A SYNTHESIS OF A NEW TYPE HETEROCYCLIC COMPOUND BY [2+2] CYCLOADDITION OF ISOQUINUCLIDINE HAVING AN ENAMINE MOIETY

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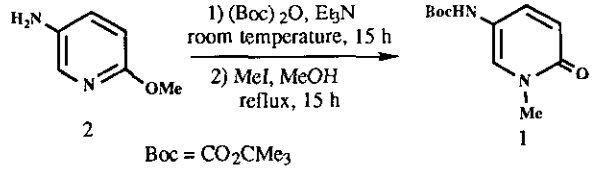
Abstract - Thermal [2+2] cycloaddition of isoquinuclidine having an enamine moiety with acetylenes regio- and stereo-selectively gave a new type of heterocyclic ring system, 7-azatricyclo[4.2.2.0^{2,5}]decanes.

Isoquinuclidines prepared by [4+2] cycloaddition of 2(1*H*)-pyridones with dienophiles[1,2] have potential as a synthetic intermediate.[1h] Therefore, we have developed a synthetic route toward this heterocyclic ring system having various substituents by the cycloaddition and a synthesis of a new type ring system using this versatile ring system.[1m,o,p] In this paper, we report [4+2] cycloaddition of the 2(1*H*)-pyridone (**1**) having a protected amino group at the 5-position with the dienophile (**3**), followed by thermal [2+2] cycloaddition of the isoquinuclidine enamine (**6**) to give a new type of heterocyclic ring system, 7-azatricyclo[4.2.2.0^{2,5}]decanes (**8a,b**).

The 2(1*H*)-pyridone (**1**) was prepared from 5-amino-2-methoxypyridine (**2**) as follows (Scheme 1).



2 1

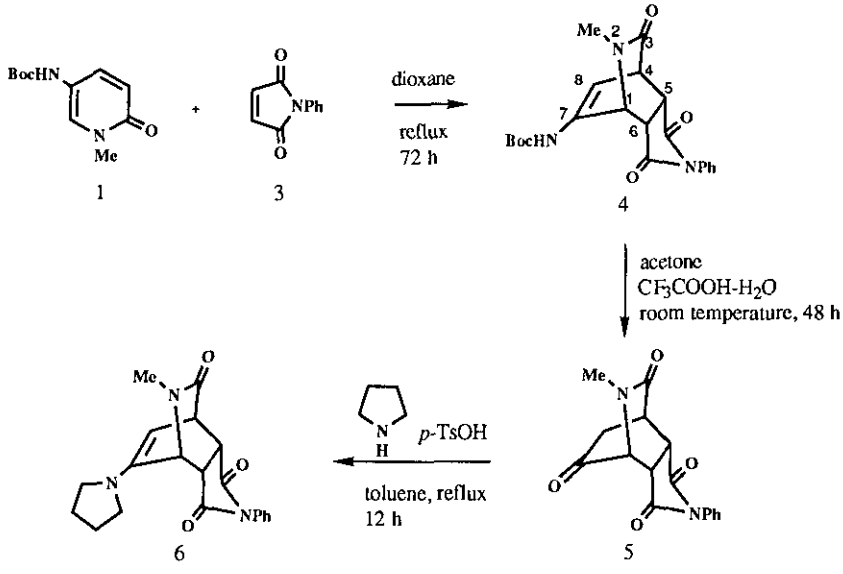
Boc = CO_2CMe_3

Scheme 1

Dedicated to Prof. Rolf Huisgen on the occasion of his 75th birthday.

Reaction of the aminopyridine (**2**) with $(Boc)_2O$ in the presence of triethylamine at room temperature followed by treatment with methyl iodide in MeOH under reflux afforded the 2(1*H*)-pyridone (**1**) (mp 134-136°C) in 68% yield from **2**.

A solution of the 2(1*H*)-pyridone (**1**) and *N*-phenylmaleimide (**3**) in dioxane was heated under reflux, and the *endo*-adduct (**4**) (mp 231-232°C) was stereoselectively obtained in 77% yield. Treatment of the adduct (**4**) with CF_3COOH-H_2O in acetone at room temperature afforded the ketone (**5**) (mp 245-246°C) in 90% yield, and then reaction of **5** and pyrrolidine with *p*-toluenesulfonic acid in toluene under reflux gave the desired isoquinuclidine enamine (**6**) (mp 173-175°C) in 72% yield (Scheme 2). The *endo* stereochemistry of **4** was determined from the coupling constant ($J_{4,5}$ = 4.3 Hz)[1m] in the ^{1}H-nmr spectrum. The structures of **1**,**4**, **5**, and **6** were confirmed by their ms, ir and ^{1}H-nmr spectral analyses.

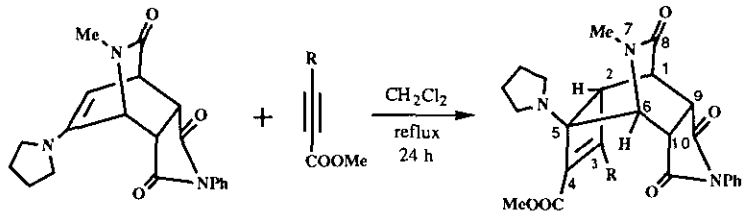


Scheme 2

Next, we investigated thermal [2+2] cycloaddition of the enamine (**6**). A solution of **6** and the acetylenes (**7a**,**b**) in dichloromethane was heated under reflux to give regio- and stereo-selectively a new type of

heterocyclic ring system, 7-azatricyclo[4.2.2.0^{2,5}]decanes [**8a** (mp 126-127°C) and **8b**(mp 217-219°C)] in 70% and 65% yields (Scheme 3).

It was suggested that the products (**8a,b**) were the 1:1 cycloadducts of **6** with **7a,b** from the ms data, and thier ir spectra showed the corresponding ester carbonyl absorptions. ^{1}H-Nmr spectra of **8a,b** revealed the characteristic signals of an isoquinuclidine system (H-1,2,6,9, and 10) and the long range coupling (*J*=1.0 Hz) between H-2 and H-6 by experiments of spin-spin decoupling, respectively. Furthermore, the coupling (*J*=0.7 Hz)[3] was observed between H-2 and H-3 in ^{1}H-nmr spectrum of **8b**. On the basis of the above spectral data, it may be deduced that the stereochemistry of **8a,b** was *cis-syn-cis* form and the methoxycarbonyl group in **8b** was at the 4-position.[4] Therefore, the structures of **8a,b** were determined to be *cis-syn-cis-N*-phenyl-3,4-dimethoxycarbonyl-7-methyl-8-oxo-5-(1-pyrrolidinyl)-7-azatricyclo-[4.2.2.0^{2,5}]dec-3-ene-9,10-dicarboximide (**8a**) and *cis-syn-cis-N*-phenyl-4-methoxycarbonyl-7-methyl-8-oxo-5-(1-pyrrolidinyl)-7-azatricyclo[4.2.2.0^{2,5}]dec-3-ene-9,10-dicarboximide (**8b**).



6

7a : R = COOMe
7*b* : R = *H*

8a : R = COOMe
8*b* : R = *H*

Scheme 3

EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Ir spectra were measured with a PERKIN ELMER 1725X spectrophotometer. ^{1}H-Nmr spectra were recorded on a JEOL JNM-PMX 60 and a JEOL JNM-GSX 400 spectrometers with TMS as an internal standard. The coupling patterns are indicated as follows: singlet=s, doublet=d, triplet=t, multiplet=m, and broad=br. Ms were taken on a Hitachi RMG-6MG and a JEOL-JNM-DX 303 spectrometers.

5-*tert*-Butoxycarbonylamino-1-methyl-2(1*H*)-pyridone (1) : To a solution of **2** (12.4 g, 0.1 mol) and triethylamine (13.0 g, 0.13 mol) in 1,4-dioxane (50 ml) was added $(Boc)_2O$ (25.0 g, 0.12 mol) in 1,4-dioxane (30 ml) at 0-5°C under N_2, and the mixture was stirred at room temperature for 15 h. After evaporation of the solvent from the reaction mixture, the residue was dissolved in AcOEt (100 ml) and then saturated aqueous $NaHCO_3$ (50 ml) was added. The mixture was stirred at room temperature for 2 h, and the organic phase was washed with water, dried ($MgSO_4$), concentrated *in vacuo* to give the crude oil (15 g). A solution of the crude oil (15.0 g) and MeI (10 ml, 0.16 mol) in MeOH (100 ml) was refluxed for 15 h, and the reaction mixture was concentrated *in vacuo* to give **1** (15.2 g, 68% from **2**), colorless prisms (isopropyl ether), mp 134-135°C. Ms m/z : 224 (M^+). *Anal.* Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found : C, 58.61; H, 7.31; N, 12.28. Ir (KBr) cm^{-1} : 1708. 1673. ^{1}H-Nmr ($CDCl_3$) δ : 1.47 (9H, s), 3.53 (3H, s), 6.60 (1H, d, J = 10.0 Hz), 7.50 (1H, dd, J = 10.0, 2.3 Hz), 7.97 (2H, br s).

***N*-Phenyl-7-*tert*-butoxycarbonylamino-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (4)** : A solution of **1** (11.2 g, 0.05 mol) and **3** (11.3 g, 0.07 mol) in 1,4-dioxane (170 ml) was refluxed for 72 h. The reaction mixture was concentrated *in vacuo* to give **4** (15.3 g, 77%), mp 231-232°C, a colorless powder (1,4-dioxane). Ms m/z : 397 (M^+). *Anal.* Calcd for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.58. Found : C, 63.49; H, 5.90; N, 10.29. Ir (KBr) cm^{-1}: 1784, 1728, 1704, 1660; ^{1}H-nmr (DMSO-d_6) δ: 1.43 (9H, s), 2.87 (3H, s), 3.23-3.63 (3H, m), 3.79 (1H, dd, J = 4.3, 6.0 Hz), 4.73 (1H, br s), 5.97 (1H, d, J = 6.0 Hz), 6.81-7.23 (2H, m), 7.25-7.57 (3H, m).

***N*-Phenyl-3,6-dioxo-2-methyl-2-azabicyclo[2.2.2]octane-7,8-*exo*-dicarboximide (5)** : To a solution of **4** (1.0 g, 2.5 mmol) and H_2O (0.5 ml) in acetone (60 ml) was added CF_3COOH (2.9 g, 25 mmol), and the mixture was stirred for 48 h at room temperature. The reaction mixture was concentrated *in vacuo* to give **5** (0.7 g, 90%), mp 245-246°C, colorless prisms (CH_2Cl_2). Ms m/z : 298 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found : C, 64.67; H, 4.58; N, 9.17.
Ir (KBr) cm^{-1}: 1780, 1709, 1650. ^{1}H-Nmr ($CDCl_3$-CF_3COOH) δ : 2.53-2.80 (2H, m), 3.13 (3H, s), 3.53-4.07 (3H, m), 4.37 (1H, d, J = 4.0 Hz), 7.00-7.27 (2H, m), 7.40-7.67 (3H, m).

***N*-Phenyl-2-methyl-3-oxo-7-(1-pyrrolidinyl)-2-azabicyclo[2.2.2]oct-7-ene-5,6-*endo*-dicarboximide (6)** : A solution of **5** (4.5 g, 15 mmol), pyrrolidine(1.4 g, 20 mmol), and *p*-toluene-

sulfonic acid monohydrate (2.9 g, 15 mmol) in toluene (50 ml) was refluxed for 12 h using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (30 ml). The solution was washed with saturated aqueous $NaHCO_3$ and water. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give **6** (3.8 g, 72 %), colorless prisms (acetone), mp 173-175 °C. Ms m/z : 351 (M^+). *Anal.* Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found : C, 68.07; H, 6.27; N, 11.91. Ir (KBr) cm^{-1}: 1770, 1702, 1650 ; ^{1}H-nmr (DMSO-d_6) δ: 1.86-1.92 (4H, m), 2.99 (3H, s), 3.04-3.10 (2H, m), 3.16-3.20 (2H, m), 3.40 (1H, dd, *J* = 3.3, 8.1 Hz), 3.62 (1H, dd, *J* = 4.4, 8.1 Hz), 3.81 (1H, dd, *J* = 3.3, 6.6 Hz), 4.43 (1H, dd, *J* = 2.6, 6.6 Hz), 4.70 (1H, dd, *J* = 2.6, 4.4 Hz), 7.08-7.11 (2H, m), 7.38-7.50 (3H, m).

General Procedure for the Preparation of the [2+2] Adducts (8a,b) : A solution of **6** (0.5 g, 1.4 mmol) and **7a** (0.27 ml, 2.1 mmol) or **7b** (0.19 ml, 2.1 mmol) in CH_2Cl_2 (10 ml) was refluxed for 24 h under N_2. The reaction mixture was concentrated *in vacuo* to dryness. The residue was subsequently purified by silica gel column chromatography using benzene as the eluent to afford the adducts (**8a,b**).

8a : 0.5 g, 70% yield, colorless prisms (benzene-isopropyl ether), mp 126-127°C. Ms m/z : 493 (M^+). *Anal.* Calcd for $C_{26}H_{27}N_3O_7$: C, 63.27; H, 5.51; N, 7.82. Found: C, 63.03; H, 5.52; N, 8.09. Ir (KBr) cm^{-1}: 1771, 1738, 1682; ^{1}H-nmr ($CDCl_3$) δ: 1.60-1.70 (4H, m), 2.58-2.80 (4H, m), 3.02 (3H, s), 3.27 (1H, d, *J*=2.9 Hz), 3.45 (2H, br s), 3.59 (1H, t, *J*=3.7 Hz), 3.80 (3H, s), 3.83 (3H, s), 4.42 (1H, d, *J*=2.6 Hz), 7.32-7.39 (3H, m), 7.44-7.48 (2H, m).

8b : 0.4 g, 65% yield, colorless prisms (benzene-ether), mp 217-219°C. Ms m/z : 435 (M^+). *Anal.* Calcd for $C_{24}H_{25}N_3O_5$: C, 66.19; H, 5.79; N, 9.65. Found: C, 66.30; H, 5.91; N, 9.34. Ir (KBr) cm^{-1}: 1769, 1713, 1689; ^{1}H-nmr ($CDCl_3$) δ: 1.59-1.70 (4H, m), 2.50-2.79 (4H, m), 2.94 (3H, s), 3.05 (1H, d, *J*=3.7 Hz), 3.38-3.43 (3H, m), 3.74 (3H, s), 4.40 (1H, d, *J*=2.6 Hz), 6.84 (1H, d, *J*=0.7 Hz), 7.28-7.48 (5H, m).

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