SYNTHESIS OF BENZO[*a*]QUINOLIZINES BY THE INTRAMOLECULAR DOUBLE MICHAEL REACTION UNDER THREE DIFFERENT CONDITIONS

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Dedicated with admiration and respect to Professor Emeritus Shigeru Oae on the occasion of his 77th birthday.

Abstract —— Benzo[*a*]quinolizines (**4A–C**) and (**5A–C**) were synthesized by the intramolecular double Michael reaction of amide esters (**3A–C**), carried out using three reagent systems; TBDMSOTf-Et_3N, TMSI-$(TMS)_2NH$, and Bu_2BOTf-$(TMS)_2NH$.

Benzo[*a*]quinolizine is a common skeleton of a number of alkaloids possessing important pharmacological activities. Recently, we developed the one step synthesis of benzo[*a*]quinolizines employing the intramolecular double Michael reaction.[1] The reaction was carried out starting with amide esters under two reaction conditions; (1) heating with TMSCl, Et_3N, and $ZnCl_2$[2a] and (2) treatment with TBDMSOTf in the presence of Et_3N under ambient temperature.[2b] It was made clear from its application to the synthesis of indolo[2,3-*a*]quinolizines that the second method is favorable because of the lower reaction temperature and the faster reaction rate, although the products are composed by diastereoisomers.[3] Therefore, we have further studied on the construction of benzo[*a*]quinolizines by way of the intramolecular double Michael reaction under various conditions. It was observed that the annulation was performed by treatment with TBDMSOTf and Et_3N to provide the mixture of stereoisomers in high yields. Furthermore, the formation of benzo[*a*]quinolizines was achieved by other two reaction conditions using TMSI[4,5] or Bu_2BOTf[6] in the presence of $(TMS)_2NH$. Here, we describe details of these results.

The amide esters (**3A–C**) were prepared in two steps from 3,4-dihydro-6,7-dimethoxyisoquinoline (**1**) as previous.[2] Treatment of **3A** with TBDMSOTf in the presence of Et_3N in $ClCH_2CH_2Cl$ at room temperature gave quantitatively a mixture of three diastereoisomeric benzo[*a*]quinolizines (entry 1). The signal due to *O*-

methyl group of the methyl ester of the major isomer was observed at 3.20 ppm in ^{1}H-nmr spectrum. The unusual high field shift of the major isomer indicates that the methyl group exists closely on two aromatic rings. The structure of the major isomer was, thus, assigned to **4A**. Although the separation of two minor isomers (**5A**) was difficult, the relationship of two hydrogens at the C(1) ant the C(11b) positions would be *trans*. The results are consistent with those of the indolo[2,3-*a*]quinolizines.[3]

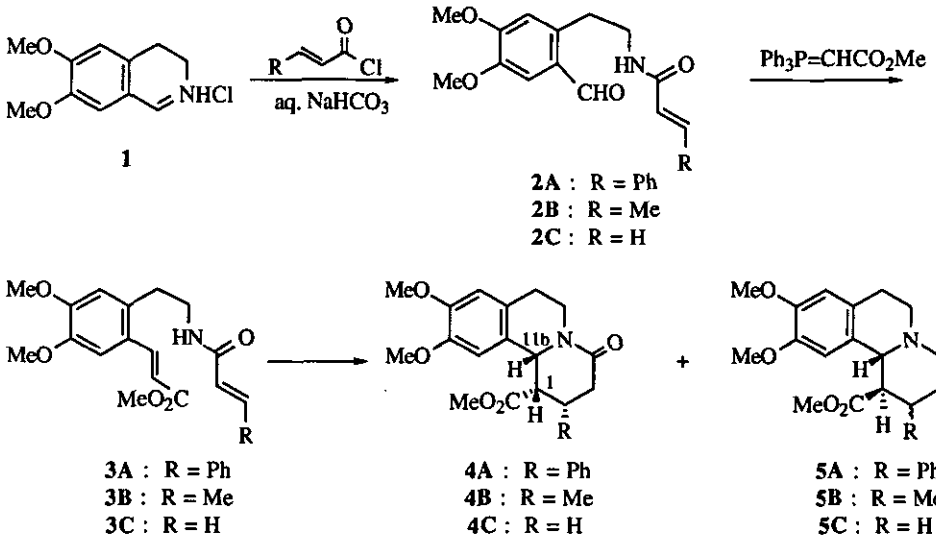

Table The intramolecular double Michael reaction of amide esters (3A–C) under three reaction conditions

entry	substrate	conditions[a]	yield (%)	ratio (4) : (5)[b]
1	**3A**	TBDMSOTf-Et_3N	100	59 : 41 (1.6 : 1)
2	**3A**	TMSI-$(TMS)_2NH$	40	70 : 30 (1 : 1)
3	**3A**	Bu_2BOTf-$(TMS)_2NH$	66	68 : 32 (1.6 : 1)
4	**3B**	TBDMSOTf-Et_3N	88	40 : 60 (4.3 : 1)
5	**3B**	TMSI-$(TMS)_2NH$	68	50 : 50 (2.8 : 1)
6	**3B**	Bu_2BOTf-$(TMS)_2NH$	48	49 : 51 (3.4 : 1)
7	**3C**	TBDMSOTf-Et_3N	85	31 : 69
8	**3C**	TMSI-$(TMS)_2NH$	13	45 : 55
9	**3C**	Bu_2BOTf-$(TMS)_2NH$	37	17 : 83

a Reactions were carried out in $ClCH_2CH_2Cl$.
b **5A** and **5B** were obtained as a mixture of two diastereoisomers. Ratios of two isomers are shown in parenthesis.

The intramolecular double Michael reaction was further achieved under two other reaction conditions, which had been effective for the intramolecular Michael-aldol reaction.[5,6] Namely, the diastereoisomeric mixture of **4A** and **5A** was obtained in 40% yield by reaction of **3A** with TMSI in the presence of $(TMS)_2NH$[4,5] in

$ClCH_2CH_2Cl$ at room temperature (entry 2). The similar treatment of **3A** with Bu_2BOTf in the presence of $(TMS)_2NH$[6] provided the mixture of **4A** and **5A** in 66% yield (entry 3). On reaction of **3B** with TBDMSOTf and Et_3N as above, a mixture of three stereoisomers (**4B**) and (**5B**) was obtained in 88% yield (entry 4). The *O*-methyl group of the methyl ester of **4B**, separated from other isomers, is resonated at a high field, 3.37 ppm, comparing with those of stereoisomers, 3.87 and 3.69 ppm. Treatments using TMSI-$(TMS)_2NH$ (entry 5) and Bu_2BOTf-$(TMS)_2NH$ (entry 6) also furnished the mixture of **4B** and **5B**, respectively.

When **3C** was treated with TBDMSOTf in the presence of Et_3N, the 31 : 69 separable mixture of two stereoisomers (**4C**) and (**5C**) was gained in 85% yield (entry 7). The signal due to the *O*-methyl group of **4C** was observed at 3.42 ppm, whereas **5C** showed that below 3.80 ppm. Two isomers (**4C**) and (**5C**) were produced by other two reaction conditions (entries 8 and 9), although yields were poor.

Thus, it has been demonstrated that stereoisomeric mixtures of benzo[*a*]quinolizines are provided by the intramolecular double Michael reaction of amide esters, conducted with three different reagent systems.

EXPERIMENTAL

Mp are uncorrected. Ir spectra were taken by JASO-IR Report-100 spectrophotometer. ^{1}H-Nmr spectra were measured on Hitachi R-3000 and Varian Gemini 300 spectrometers. Chemical shifts were reported as δ_H values relative to internal TMS. Ms spectra were recorded on JEOL-JMS-DX-303 and JEOL-JMS-AX-500 spectrometers.

Methyl 2-(2-Cinnamamidoethyl)-4,5-dimethoxycinnamate (3A). To a vigorously stirred mixture of 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride (**1**) (502 mg, 2.21 mmol), CH_2Cl_2 (7 ml) and saturated aqueous $NaHCO_3$ (12 ml) at room temperature was added a solution of cinnamoyl chloride (478 mg, 2.87 mmol) in CH_2Cl_2 (5 ml) during 45 min. After being stirred for 2 h at the same temperature, followed by dilution with CH_2Cl_2, the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give the crude aldehyde (**2A**), which was used in the following reaction without purification.

A mixture of the above product and $Ph_3P{=}CHCO_2Me$ (738 mg, 3.21 mmol) in MeCN (14 ml) was stirred for 13 h at room temperature and then heated for 1 h under reflux. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$-MeOH (99.5 : 0.5 v/v) afforded a yellowish solid, which was triturated with hexane to provide the amide ester (**3A**) (494 mg,

57%) as a colorless powder, mp 160–162 °C. Ir ($CHCl_3$) ν max cm^{-1} 1700, 1670, 1640, 1605. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* = 15.7 Hz, olefinic H), 7.61 (1H, d, *J* = 15.7 Hz, olefinic H), 7.40–7.32 (5H, m, Ph), 7.08 (1H, s, Ar H), 6.74 (1H, s, Ar H), 6.32 (1H, d, *J* = 15.7 Hz, olefinic H), 6.30 (1H, d, *J* = 15.7 Hz, olefinic H), 5.79–5.70 (1H, br s, NH) 3.90 (3H, s, OMe), 3.88 (3H, s, OMe), 3.77 (3H, s, OMe), 3.57 (2H, q, *J* = 7.0 Hz, NHC*H*$_2$), 3.03 (2H, t, *J* = 7.0 Hz, ArC*H*$_2$). HRms m/z: Calcd for $C_{23}H_{25}NO_5$ (M^+) 395.1731. Found 395.1733.

Methyl 2-(2-Crotonamidoethyl)-4,5-dimethoxycinnamate (3B). By the same procedure as above, the amide ester (**3B**) was obtained in 41% yield from **1** as a colorless powder, mp 133–135 °C. Ir ($CHCl_3$) ν max cm^{-1} 1700, 1680, 1640, 1605. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 15.9 Hz, ArC*H*=), 7.07 (1H, s, ArH), 6.84 (1H, dq, *J* = 14.7, 7.0 Hz, MeC*H*=), 6.71 (1H, s, ArH), 6.29 (1H, d, *J* = 15.9 Hz, MeO_2CCH=), 5.72 (1H, dd, *J* = 14.7, 1.5 Hz, –HNCOC*H*=), 5.53 (1H, br s, NH), 3.90 (3H, s, OMe), 3.88 (3H, s, OMe), 3.81 (3H, s, OMe), 3.49 (2H, q, *J* = 7.3 Hz, NHC*H*$_2$), 2.97 (2H, t, *J* = 7.3 Hz, ArC*H*$_2$), 1.84 (3H, br d, =CH*Me*). HRms m/z: Calcd for $C_{18}H_{23}NO_5$ (M^+) 333.1575. Found 333.1577.

Methyl 2-(2-Acrylamidoethyl)-4,5-dimethoxycinnamate (3C). Similarly, the amide ester (**3C**) was prepared in 51% yield from **1** as a colorless powder, mp 140–141 °C. Ir ($CHCl_3$) ν max cm^{-1} 1700, 1670, 1630, 1605. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 7.93 (1H, d, 15.7 Hz, ArC*H*=), 7.08 (1H, s, ArH), 6.71 (1H, s, ArH), 6.28 (1H, d, *J* = 15.7 Hz, MeO_2CCH=), 6.27 (1H, dd, *J* = 17.0, 1.7 Hz, =C*H*H), 6.03 (1H, dd, *J* = 17.0, 10.5 Hz, –C*H*=CH_2), 5.64 (1H, dd, *J* = 10.5, 1.7 Hz, =CH*H*), 5.64–5.58 (1H, m, NH), 3.89 (3H, s, OMe), 3.88 (3H, s, OMe), 3.81 (3H, s, OMe), 3.56–3.51 (2H, m, NHC*H*$_2$), 3.30 (2H, t, *J* = 7.0 Hz, $ArCH_2$). HRms m/z: Calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1418. Found 319.1420.

Methyl 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-4-oxo-2-phenyl-2*H*-benzo[*a*]quinolizine-1-carboxylates (4A and 5A). (Method A) To a stirred solution of the amide ester (**3A**) (33.0 mg, 83.4 μmol) in dry $ClCH_2CH_2Cl$ (3.3 ml) at room temperature were added Et_3N (23.3 μl 167 μmol) and TBDMSOTf (28.9 μl 125 μmol), and the mixture was stirred for 21 h at the same temperature. After dilution with $CHCl_3$, the resulting mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with benzene-acetone (5 : 1 v/v) to afford a mixture of **4A** and **5A** (33.0 mg, 100%) in a ratio of 59 : 41.

Further purification using preparative tlc gave **4A** as a polar compound, and **5A** was obtained from a less polar fraction as a 1.6 : 1 mixture of two diastereoisomers. **4A**: Ir ($CHCl_3$) ν max cm^{-1} 1740, 1640. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 7.39–7.21 (5H, m, Ph), 6.65 (1H, s, Ar H), 6.59 (1H, s, Ar H), 5.30–5.09 (2H, m), 3.92–3.78 (1H, m), 3.85 (3H, s, OMe), 3.81 (3H, s, OMe), 3.68–3.51 (2H, m), 3.20 (3H, s, CO_2Me), 2.97–2.82 (1H, m), 2.81–2.68 (2H, m), 2.59 (1H, br d, *J* = 15.0 Hz). HRms m/z: Calcd for $C_{23}H_{25}NO_5$ (M^+) 395.1731. Found 395.1733. **5A**: Ir ($CHCl_3$) ν max cm^{-1} 1735, 1640. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 7.37–7.28 (3.10H, m, Ph), 7.24–7.13 (1.90H, m, Ph), 6.68–6.67 (1.62H, br s, ArH), 6.61 (0.38H, s, ArH), 5.11–5.03 (1.24H, m), 4.71–4.65 (0.38H, m), 4.60–4.52 (0.38H, m), 3.88 (1.14H, s, OMe), 3.87 (1.86H, s, OMe), 3.82 (1.14H, s, OMe), 3.77 (1.86H, s, OMe), 3.47 (1.14H, s, CO_2Me), 3.46–3.40 (1H, m), 3.38 (1.86H, s, CO_2Me), 3.25–2.64 (m, 6H). HRms m/z: Calcd for $C_{23}H_{25}NO_5$ (M^+) 395.1731. Found 395.1760.

(Method B) To a stirred solution of **3A** (34.5 mg, 87.2 μmol) and $(TMS)_2NH$ (46.0 μl, 218 μmol) in dry $ClCH_2CH_2Cl$ (0.7 ml) under cooling with ice was added TMSI (27.3 μl, 192 μmol). The mixture was stirred for 10 min at the same temperature and for 19 h at room temperature. The same work-up, followed by purification of the resulting mixture as above, gave a mixture of **4A** and **5A** (13.8 mg, 40%) in a ratio of 7 : 3.

(Method C) To a stirred solution of **3A** (34.0 mg, 86.0 μmol) and $(TMS)_2NH$ (72.6 μl, 344 μmol) in dry $ClCH_2CH_2Cl$ (0.7 ml) under cooling with ice was added 1.0 M Bu_2BOTf in CH_2Cl_2 (258 μl, 258 μmol). After being stirred for 10 min, the mixture was further stirred for 19 h at room temperature. The same work-up, followed by purification as above, afforded a mixture of **4A** and **5A** (22.2 mg, 66%) in a ratio of 68 : 32.

Methyl 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-4-oxo-2-methyl-2*H*-benzo[*a*]quinolizine-1-carboxylates (4B and 5B). By the three methods as described above, the amide ester (**3B**) was converted into **4B** and **5B**. Yields and ratios of diastereoisomers are recorded in the Table. **4B**: Ir ($CHCl_3$) ν max cm^{-1} 1740, 1640. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 6.65 (1H, s, ArH), 6.59 (1H, s, ArH), 5.08–5.04 (1H, m), 4.90 (1H, d, *J* = 4.3 Hz), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 3.41 (1H, dd, *J* = 4.3, 3.7 Hz), 3.37 (3H, s, CO_2Me), 2.89–2.83 (1H, m), 2.72–2.67 (1H, m), 2.56 (1H, d, *J* = 16.8 Hz), 2.55 (1H, d, *J* = 16.8 Hz), 2.45–2.33 (2H, m), 1.10 (3H, d, *J* = 4.3 Hz, 2–Me). HRms m/z:

Calcd for $C_{18}H_{23}NO_5$ (M^+) 333.1575. Found 333.1576. **5B**: Ir ($CHCl_3$) ν max cm^{-1} 1735, 1640. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 6.72 (0.19H, s, ArH), 6.70 (0.81H, s, ArH), 6.68 (0.19H, s, ArH), 6.66 (0.81H, s, ArH), 5.03–4.93 (1H, m), 4.56–4.41 (1H, m), 3.91 (0.57H, s, OMe), 3.89 (0.57H, s, OMe), 3.87 (2.43H, s, CO_2Me), 3.83 (2.43H, s, OMe), 3.80 (2.43H, s, OMe), 3.69 (0.57H, s, CO_2Me), 3.15–3.04 (1H, m), 3.01–2.85 (1H, m), 2.74–2.61 (3H, m), 2.17–2.03 (1H, m), 1.86–1.80 (1H, m), 1.10 (0.57H, d, J = 6.6 Hz, 2–Me), 1.03 (2.43H, d, J = 6.6 Hz, 2–Me). HRms m/z: Calcd for $C_{18}H_{23}NO_5$ (M^+) 333.1575. Found. 333.1582.

Methyl 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-4-oxo-2*H*-benzo[*a*]quinolizine-1-carboxylates (4C and 5C). By the three methods as described above, the amide ester (**3C**) was transformed into **4C** and **5C**. Yields and ratios were reported in the Table. **4C**: Ir ($CHCl_3$) ν max cm^{-1} 1735, 1650. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 6.61 (1H, s, ArH), 6.59 (1H, s, ArH), 4.98–4.92 (1H, m), 4.86 (1H, br d, J = 4.7 Hz), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 3.42 (3H, s, CO_2Me), 3.49–3.45 (1H, m), 2.90–2.61 (2H, m), 2.57–2.53 (3H, m), 2.25–2.18 (2H, m). HRms m/z: Calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1418. Found 319.1414. **5C**: Ir ($CHCl_3$) ν max cm^{-1} 1735, 1640. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ 6.65 (1H, s, ArH), 6.58 (1H, s, ArH), 5.04 (1H, br d, J = 8.1 Hz), 4.62–4.56 (1H, m), 3.86 (3H, s, OMe), 3.81 (3H, s, OMe), 3.80 (3H, s, OMe), 3.03–2.89 (3H, m), 2.71–2.55 (2H, m), 2.43–2.15 (1H, m), 2.13–2.02 (2H, m). HRms m/z: Calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1418. Found 319.1403.

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