Stereocontrolled Synthesis of Indolo[2,3-*a*]quinolizines by Intramolecular Double Michael Reaction: Proof for Stepwise Mechanism

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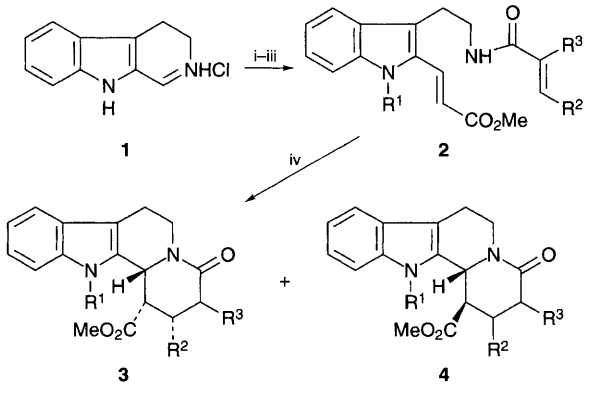
Indolo[2,3-*a*]quinolizines **3** were stereoselectively synthesized by the intramolecular double Michael reaction of amide esters **2**, the indole nitrogen of which was protected with a tosyl group, using $Bu^tMe_2SiOSO_2CF_3$ in the presence of Et_3N.

Indolo[2,3-*a*]quinolizine is a common framework of a number of indole alkaloids and biologically active compounds. Therefore, the development of efficient methods for construction of the skeleton is an important problem. Previously, we reported the preparation of a benzo[*a*]quinolizine derivative by the intramolecular double Michael reaction[1] of ethyl (*E*,*E*)-2-(2-cinnamamidoethyl)-4,5-dimethoxycinnamate with trialkylsilyl trifluoromethanesulfonate in the presence of Et_3N.[2] The stereochemistry of the product was tentatively assigned from mechanistic consideration. The present study has established a facile and stereocontrolled synthesis of indolo[2,3-*a*]quinolizine derivatives and a stepwise mechanism for the cyclization reaction.

Amide esters **2a**, **c**, **e**, **g** and **i** were prepared, in two steps,[2] from 3,4-dihydro-β-carboline hydrochloride **1**, and the NH of the indole moiety was selectively protected with a tosyl group to give **2b**, **d**, **f**, **h** and **j** in reasonable yields (Scheme 1). Although treatment of acrylamide **2a** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and Et_3N[2] afforded no desired product (entry 1 in Table 1), the corresponding tosylate **2b** was converted into a *ca.* 4:1 mixture of indolo[2,3-*a*]quinolizines **3b** and **4b** by the same treatment in CH_2Cl_2 (entry 2) and in $ClCH_2CH_2Cl$ (entry 3).† The ester methyl group of the major product **3b** resonated at δ 3.29, compared with δ 3.86 for **4b**, in the ^1H NMR spectrum. The stereostructure of **3b** was confirmed by X-ray analysis.‡ The ORTEP representation (Fig. 1) indicates that the methyl group of the ester functionality is located under the indole ring. It is noteworthy that the carbonyl group of the ester is parallel to the carbonyl group of the lactam. It is clear from the stereochemistry of **3b** that the geometry of the α,β-unsaturated ester group was not retained during the cyclization.

(*E*)-Crotonamide **2c** gave **3c** together with both isomers of **4c**, *ca.* 3:2 (entries 4 and 5), while the (*Z*)-isomer of **2c** led to **3c** and **4c**, 81:19 (entry 6). This result clearly proves that the cyclization proceeds *via* a common intermediate in a stepwise manner.



Scheme 1 *Reagents and conditions*: i, RCOCl, sat. $NaHCO_3$; ii, $Ph_3P{=}CHCO_2Me$; iii, NaH, TsCl, DMF; iv, $Bu^tMe_2SiOSO_2CF_3$, Et_3N, room temp.

The isomer **3d** possessing *cis*-orientated hydrogens at the C-1 and the C-12b positions was selectively obtained from the tosylate **2d** (entries 7 and 8). The predominant production of **3f** was also observed in the case of tosylate **2f** (entries 11 and 12), while the unprotected indole derivative **2e** of (*E*)-cinnamamide resulted in poor selectivity (entries 9 and 10).

Table 1 Intramolecular double Michael reaction forming indolo[2,3-*a*]-quinolizines[a]

Entry	Substrate	R1	R2	R3	Solvent[b]	Yield (%)	3:4
1	**2a**	H	H	H	A	0	—
2	**b**	Ts	H	H	A	45	82:18
3	**b**	Ts	H	H	B	42	76:24
4	**c**	H	Me	H	A	60	60:40[c]
5	**c**	H	Me	H	B	54	54:46[d]
6	**c**[e]	H	Me	H	A	42	81:19[f]
7	**d**	Ts	Me	H	A	90	87:13[g]
8	**d**	Ts	Me	H	B	94	83:17[h]
9	**e**	H	Ph	H	A	89	69:31[i]
10	**e**	H	Ph	H	B	86	63:37[j]
11	**f**	Ts	Ph	H	A	71	86:14[k]
12	**f**	Ts	Ph	H	B	80	84:16[l]
13	**g**	H	$SiMe_3$	H	A	<2	—
14	**g**	H	$SiMe_3$	H	B	33	36:64[m]
15	**h**	Ts	$SiMe_3$	H	A	27	99:1
16	**h**	Ts	$SiMe_3$	H	B	62	98:2
17	**i**	H	H	Me	A	34	<1:99[n]
18	**i**	H	H	Me	B	42	<1:99[o]
19	**j**	Ts	H	Me	A	0	—

[a] All reactions were carried out at ambient temperature using $Bu^tMe_2SiOSO_2CF_3$ (1.5 equiv.) and Et_3N (2.0 equiv.). [b] A = CH_2Cl_2, B = $ClCH_2CH_2Cl$. [c] **4c** (2β-Me:2α-Me = 1.7:1). [d] **4c** (2β-Me:2α-Me = 1.5:1). [e] The (*Z*)-isomer of **2c**. [f] **4c** (2β-Me:2α-Me = 2:1). [g] **4d** (2β-Me:2α-Me = 2.1:1). [h] **4d** (2β-Me:2α-Me = 2.25:1). [i] **4e** (2β-Ph:2α-Ph = 4.8:1). [j] **4e** (2β-Ph:2α-Ph = 3.8:1). [k] **4f** (2β-Ph:2α-Ph = 6:1). [l] **4f** (2β-Ph:2α-Ph = 5:1). [m] **4g** (2β-$SiMe_3$:2α-$SiMe_3$ = 1:1.7). [n] **4i** (3β-Me:3α-Me = 1.9:1). [o] **4i** (3β-Me:3α-Me = 2.7:1).

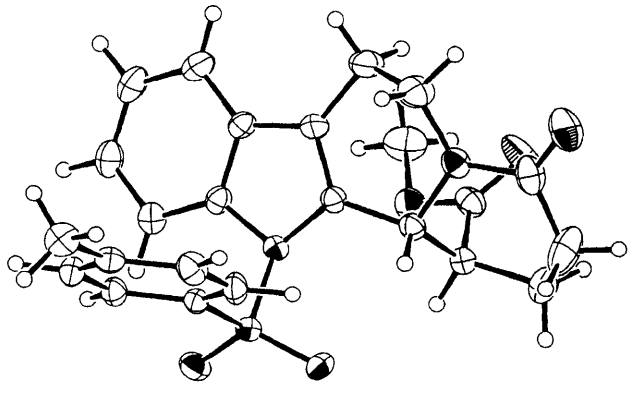


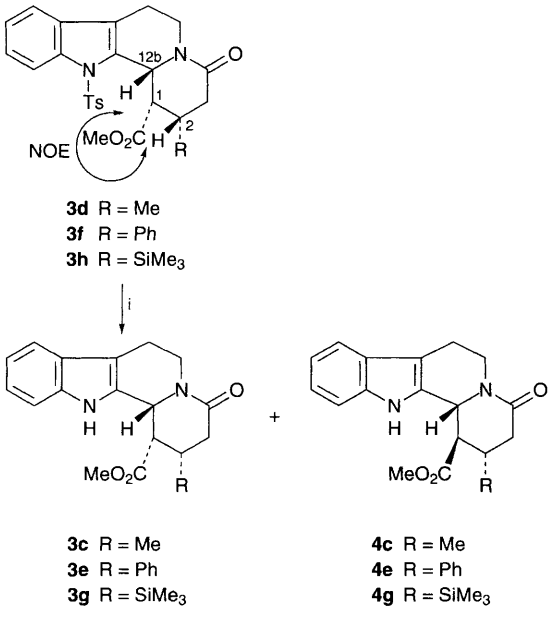
Fig. 1 View of the molecular structure of **3b**

The cyclization of (*E*)-β-trimethylsilylacrylamides **2g** and **2h** was sluggish using CH_2Cl_2 as solvent (entries 13 and 15), but the reaction proceeded smoothly in $ClCH_2CH_2Cl$ (entries 14 and 16). Tosylate **2h** was transformed into **3h** in a highly stereoselective manner (entry 16).

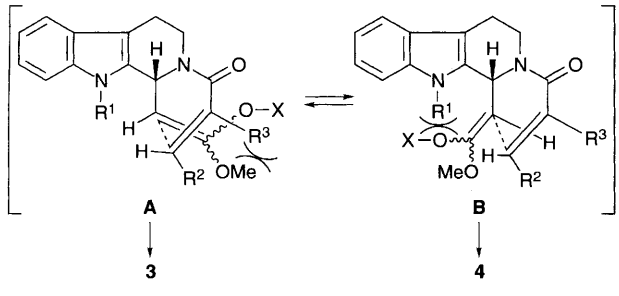
It is interesting that one of two possible isomers was obtained in the formation of **3**. The stereochemistries of the products **3c–h** were determined by the chemical shift of the ester methyl group and the NOE between hydrogens at the C-2 and the C-12b positions. The tosyl group was removed by treatment with Mg in MeOH[3] at *ca.* 50 °C (Scheme 2). An 83 : 17 mixture of **3c** and **4c** (2α-Me) was produced from **3d** in 95% yield, while **3f** and **3h** led to a 2 : 3 mixture of **3e** and **4e** (2α-Ph) in 86% yield and a 91 : 9 mixture of **3g** and **4g** (2α-$SiMe_3$) in 91% yield, respectively. Epimerization at the C-1 position with $Mg(OMe)_2$ was demonstrated by the use of CD_3OD as solvent.

The formation of stereoisomers could be explained by the conformation of intermediates (Scheme 3). The conformation **B**, leading to 2α-substituted **4**, is disfavoured due to the presence of the tosyl group and the conformation **A** leading to **3** would be preferred for tosylates.

A mixture of two isomers of **4i** was selectively formed from methacrylamide **2i** (entries 17 and 18), since the steric interaction with the methyl group makes **A** a disfavoured one.



Scheme 2 *Reagents and conditions*: i, Mg, MeOH, *ca.* 50 °C



Scheme 3

The reason why no cyclized product was obtained from the tosylate **2j** (entry 19) would be that a proper conformation for the second Michael reaction could not be formed.

Received, 10th July 1995; Com. 5/04468E

Footnotes

† All new compounds gave satisfactory spectral data (IR, NMR, and MS) and microanalytical or high resolution MS data.

Selected data for **3b**: δ_H (500 MHz, $CDCl_3$) 2.29 (3 H, s, Ar*Me*), 3.29 (3 H, s, OMe), 4.00–4.10 (1 H, m, 1-H), 5.00–5.10 (1 H, m, 6-H), 5.34 (1 H, d, *J* 2.2 Hz, 12b-H). For **4b**: δ_H (300 MHz, $CDCl_3$) 2.28 (3 H, s, Ar*Me*), 3.86 (3 H, s, OMe), 4.07 (1 H, br s, 1-H), 5.00–5.10 (1 H, m, 6-H), 5.64 (1 H, br s, 12b-H). For **3c**: δ_H (300 MHz, $CDCl_3$) 1.10 (3 H, d, *J* 6.2 Hz, 2-Me), 3.38 (4 H, br s, OMe and 1-H), 5.04 (1 H, d, *J* 4.8 Hz, 12b-H), 5.20–5.30 (1 H, m, 6-H), 8.11 (1 H, br s, NH). For **4c** (2α-Me): δ_H (400 MHz, $CDCl_3$) 1.04 (3 H, d, *J* 6.4 Hz, 2-Me), 2.59 (1 H, t, *J* 10.3 Hz, 1-H), 3.92 (3 H, s, OMe), 5.06 (1 H, d, *J* 10.3 Hz, 12b-H), 5.13 (1 H, d, *J* 8.8 Hz, 6-H), 8.13 (1 H, br s, NH). For **3d**: δ_H (300 MHz, $CDCl_3$) 1.11 (3 H, d, *J* 5.9 Hz, 2-Me), 2.28 (3 H, s, Ar*Me*), 3.24 (3 H, s, OMe), 3.95–4.00 (1 H, m, 1-H), 5.10–5.25 (1 H, m, 6-H), 5.35–5.40 (1 H, m, 12b-H). For **3e**: δ_H (300 MHz, $CDCl_3$) 3.20 (3 H, s, OMe), 5.21 (1 H, br d, *J* 4.8 Hz, 12b-H), 5.20–5.35 (1 H, m, 6-H), 8.17 (1 H, br s, NH). For **4e** (2α-Ph): δ_H (300 MHz, $CDCl_3$) 3.52 (3 H, s, OMe), 5.19 (2 H, br d, *J* 9.2 Hz, 12b- and 6-H), 8.23 (1 H, br s, NH). For **3f**: δ_H (300 MHz, $CDCl_3$) 2.29 (3 H, s, Ar*Me*), 3.03 (3 H, s, OMe), 3.69 (1 H, ddd, *J* 12.8, 7.0 and 4.0 Hz, 2-H), 4.33 (1 H, dd, *J* 4.0 and 3.3 Hz, 1-H), 5.15–5.30 (1 H, m, 6-H), 5.58 (1 H, br d, *J* 3.3 Hz, 12b-H). For **4f** (2α-Ph): δ_H (300 MHz, $CDCl_3$) 2.28 (3 H, s, Ar*Me*), 3.48 (3 H, s, OMe), 4.15–4.20 (1 H, m, 1-H), 5.05–5.20 (1 H, m, 6-H), 5.50–5.55 (1 H, m, 12b-H). For **3g**: δ_H (300 MHz, $CDCl_3$) 0.07 (9 H, s, $SiMe_3$), 1.55 (1 H, ddd, *J* 13.6, 5.9 and 3.3 Hz, 2-H), 3.33 (3 H, s, OMe), 3.40–3.45 (1 H, m, 1-H), 5.00 (1 H, br d, *J* 4.4 Hz, 12b-H), 5.20–5.30 (1 H, m, 6-H), 8.05 (1 H, br s, NH). For **4g** (2α-$SiMe_3$): δ_H (300 MHz, $CDCl_3$) 0.05 (9 H, s, $SiMe_3$), 1.63 (1 H, dt, *J* 11.7 and 5.1 Hz, 2-H), 3.87 (3 H, s, OMe), 5.05–5.15 (2 H, m, 12b- and 6-H), 8.18 (1 H, br s, NH). For **3h**: δ_H (500 MHz, $CDCl_3$) 0.07 (9 H, s, $SiMe_3$), 1.63 (1 H, ddd, *J* 12.8, 6.7 and 3.1 Hz, 2-H), 2.29 (3 H, s, Ar*Me*), 3.22 (3 H, s, OMe), 4.08 (1 H, br t, *J* 3.1 Hz, 1-H), 5.15–5.20 (1 H, m, 6-H), 5.33 (1 H, br s, 12b-H). For **4i** (3β-Me): δ_H (500 MHz, $CDCl_3$) 1.32 (3 H, d, *J* 6.7 Hz, 3-Me), 3.91 (3 H, s, OMe), 5.13 (2 H, br d, *J* 9.2 Hz, 12b- and 6-H). For **4i** (3α-Me): δ_H (300 MHz, $CDCl_3$) 1.26 (3 H, d, *J* 7.1 Hz, 3-Me), 3.90 (3 H, s, OMe), 5.00–5.10 (1 H, m, 6-H), 5.12 (1 H, d, *J* 9.9 Hz, 12b-H).

‡ *Crystal data* for **3b**: mp 207–208 °C, $C_{24}H_{24}N_2O_5S$, M = 452.53, triclinic, space group $P\bar{1}$ (No. 2), a = 8.858(9), b = 15.444(3), c = 8.035(2) Å, α = 98.26(2), β = 92.01(4), γ = 81.43(4)°, V = 1075(1) Å^3, Z = 2, D_c = 1.40 g cm^{-3}, intensities were recorded for 4952 unique reflections ($2\theta_{max}$ = 55°) on Rigaku AFC5R diffractometer using graphite monochromated Mo-Kα-radiation. 3744 reflections [$I_o > 3\sigma(I_o)$] were used for the structure solution. The structure was solved by the direct method using Rigaku TEXSAN Programs (TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985). After the block-diagonal least-squares refinement for non-hydrogen atoms with anisotropic thermal parameters, the hydrogen atoms were calculated geometrically and also verified from the difference Fourier map and then included in the refinement with isotropic thermal parameters. The final R factor was 0.048 (R_w = 0.063).

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 M. Ihara and K. Fukumoto, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1010.
2 M. Ihara, T. Kirihara, A. Kawaguchi, M. Tsuruta, K. Fukumoto and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1719.
3 A. C. Brown and L. A. Carpino, *J. Org. Chem.*, 1985, **50**, 1749.