A DIASTEREOSELECTIVE SYNTHESIS OF 7-ARYLPYRIMIDO[6,1-a]ISOQUINOLINES THROUGH N-ACYLIMINIUM ION CYCLIZATION

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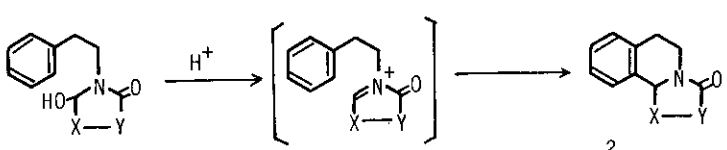
Abstract —— Reduction of ureas (4 and 9a) with diisobutylaluminum hydride, followed by cyclization with formic acid gave the corresponding 1- and 7-substituted pyrimido[6,1-a]isoquinolines (5 and 10a), respectively, with diastereoselectivity. In a similar fashion, 7-aryl-1-methyl analogues (10b,c) were obtained from ureas (9b,c) accompanied by the formation of uncyclized formates (11a,b), respectively.

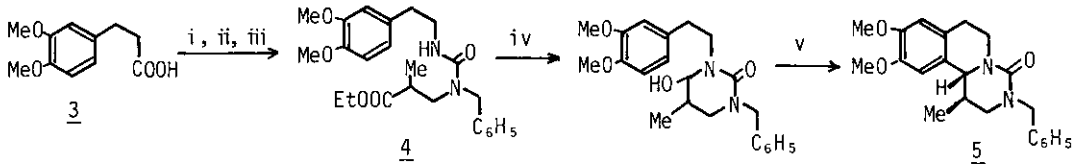
π Cyclization of several kinds of N-acyliminium ions have been used for a synthesis of wide variety of heterocyclic systems[1]. From Pioneering work of Speckamp[1a-c], and the studies of others[1d-i], such cyclizations have been found to achieve remarkable stereocontrol in a asymmetric synthesis. N-Acyliminium ion cyclizations onto aromatic ring have been used for a synthesis of heterocyclic fused tetrahydroisoquinolines (2) from 1. Previously we reported a diastereoselective synthesis of 1- and 6-aryl[4,3-a]isoquinolines[2] by this method. In continuation of our previous studies in connection with our interest in 4-aryl-1,2,3,4-tetrahydroisoquinolines because of their potentially biological activities[3], we investigated a synthesis of 7-arylpyrimido[6,1-a]isoquinolines according to the method previously reported[4]. Heterocycles fused with pyrimidine are of interest from pharmacological point of view[5] and many of their derivatives are useful drugs. 1-Substituted pyrimido[6,1-a]isoquinoline was also prepared to examine whether cyclization proceeds with stereoselectivity. The results of our studies are described in this paper.



1 2

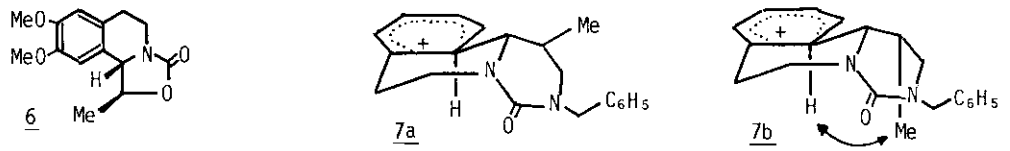
a: X-Y=CH_2-S; b: CH_2-O; c: CH_2N; d: CH_2N-CH_2; e: CH_2CH_2N

At first, we described a synthesis of 1-methyl-1,11b-trans-pyrimido[6,1-a]isoquinoline (5). The urea (4), the precursor of the N-acyliminium ion which undergoes cyclization to 5, is easily obtained from 3,4-dimethoxyphenylpropionic acid (3) via conversion to acid azide followed by reaction with ethyl β-benzylamino-α-methylpropionate. Reduction of 4 with diisobutylaluminum hydride in toluene at -78°C, followed by cyclization with formic acid yielded 5 as a single diastereomer without formation of the alternative stereoisomer. In this reaction, arylation proceeds from the opposite side of methyl group, as in the formation of 1-methyloxazolo[4,3-a]isoquinoline (6)[2a], to take the transition state (7a) which should be more favorable than the alternative one (7b).



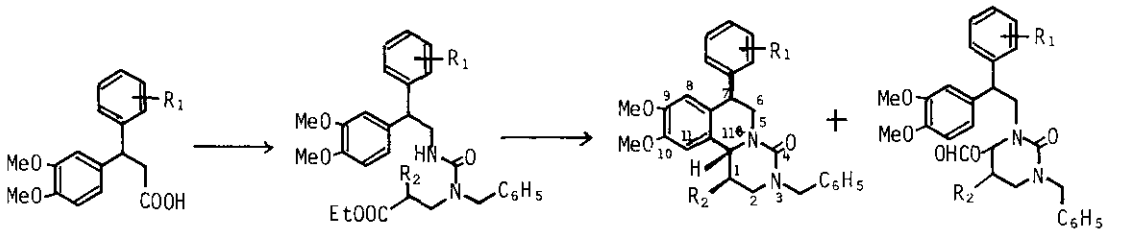
3 4 5

i) $Et_3N/ClCOOEt$, ii) NaN_3, iii) $EtOOCCH(CH_3)CH_2NHCH_2C_6H_5$, iv) DIBAH, v) HCOOH



6 7a 7b

In the same manner, the urea (9a), obtained from the acid (8a)[2c], was converted to the desired 7-phenylpyrimidoisoquinoline (10a) with high diastereoselectivity without formation of the alternative isomer. In the ^1H NMR ($CDCl_3$) spectrum, the characteristic signals were observed at δ 2.97 (d,d, J=10.5 and 13.5 Hz, ax. 6-H), 4.22 (d,d, J=5 and 10 Hz, 11b-H) and 4.89 (d,d, J=5 and 13.5 Hz, eq. 6-H). The vicinal coupling constant for $J_{6,7}$ indicates that the relative configuration of 7-H and 11b-H is trans from the consideration of the Dreiding molecular model and the Karplus relation[6].



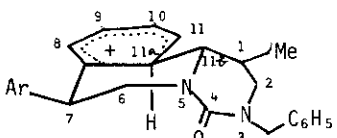
8a: R_1=H
8b: R_1=3,4-$(OMe)_2$

9a: R_1=R_2=H
9b: R_1=H, R_2=Me
9c: R_1=3,4-$(OMe)_2$, R_2=Me

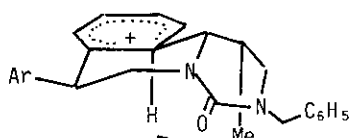
10a: R_1=R_2=H
10b: R_1=H, R_2=Me
10c: R_1=3,4-$(OMe)_2$, R_2=Me

11a: R_1=H, R_2=Me
11b: R_1=3,4-$(OMe)_2$ R_2=Me

In the next stage, we examined the same reaction by using ureas (9b,c) derived from 8a and 8b. Reduction of 9b,c with diisobutylaluminum hydride, followed by cyclization with formic acid at room temperature yielded the corresponding 7-aryl-1-methylpyrimidoisoquinolines (10b,c), respectively, as a single diastereomer, accompanied by the formation of uncyclized formates (11a,b). Treatment of 11a,b with formic acid at higher temperature (60°C) resulted in a recovery of 11a,b and the formation of 10b,c was not observed. The minimum steric 1,3-interaction between 11a-H and phenyl group (or 11a-H and methyl group) in the transition state (12) can accounted for a diastereoselective synthesis of these cyclization products. Only 7,11a-trans-11a,1-trans-intermediate (12a) in the transition state yields the cyclization products and another intermediate (12b) gave rise to a formation of uncyclized formate (11).



12a



12b

EXPERIMENTAL

Melting points are not corrected. ^{1}H NMR spectra were taken on a Varian EM 390 instrument. Mass spectra were taken at an ionizing voltage of 70 eV on a Hitachi RMU-7L instrument.

General Procedure for a synthesis of Ureas (4 and 9) To a stirred mixture of carboxylic acid (3 or 8: 30 mmol) and Et_3N (5.05 g, 50 mmol) in acetone (40 ml) was added ClCOOEt (3.27 g, 30 mmol) under ice-cooling. After the stirring had been continued for 0.5 h at the same temperature, a solution of NaN_3 (3.25 g, 50 mmol) in H_2O (4 ml) was added. After 1 h, the mixture was diluted with H_2O and extracted with toluene. The extract was dried (Na_2SO_4 and evaporated to 50 ml and heated in the presence of ethyl α-methyl-β-benzylaminopropionate (7.29 g, 33 mmol)(for preparation of 9a, 6.83 g, 33 mmol of ethyl β-benzylaminopropionate was used) under reflux for 14 h. The solvent was evaporated and the remaining residue was chromatographed on silica gel (30 g). Elution with benzene gave the corresponding urea.

4: This compound was obtained in 76 % yield, mp 108-110°C, ^{1}H NMR ($CDCl_3$) δ 1.09 (3H, t, J=7 Hz), 1.22 (3H, t, J=7.5 Hz), 2.66-2.80 (2H, m), 3.06-3.68 (5H, m), 3.83 (6H, s), 4.10 (2H, q, J=7.5 Hz), 4.33 (1H, d, J=13 Hz), 4.57 (1H, d, J=13 Hz), 6.76 (3H, s), 7.13-7.32 (5H, m). Anal. Calcd for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; N, 6.54. Found: C, 67.37; H, 7.53; N, 6.61.

9a: This compound was obtained as an oil in 67 % yield, ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, J=7.5 Hz), 2.38-2.50 (2H, m), 3.41-3.57 (2H, m), 3.77-3.97 (2H, m), 3.82 (3H, s), 3.86 (3H, s), 4.09 (2H, q, J=7.5 Hz), 4.39 (2H, s), 6.80 (3H, s), 7.06-7.33 (10H, m). Signals due to $NHCH_2CHAr_2$ are con-

cealed beneath CH_3O signals at δ around 3.8.

9b: This compound was obtained as an oil in 65 % yield, ^1H NMR ($CDCl_3$) δ 1.02 (3H, d, J=7 Hz), 1.18 (3H, t, J=7.5 Hz), 2.51-2.83 (1H, m), 3.23-3.48 (2H, m), 3.74 (3H, s), 3.78 (3H, s), 4.01 (2H, q, J=7.5 Hz), 4.23 (1H, d, J=13 Hz), 4.50 (1H, d, J=13 Hz), 6.78 (3H, broad s), 7.21-7.23 (10H, m). Signals due to $HNCH_2CHAr$ are concealed beneath CH_3O signals at δ around 3.8.

General Procedure for a Synthesis of Pyrimido[6,1-a]isoquinolines (5) and (10) To a stirred solution of 4 (or 9) (10 mmol) in toluene (50 ml) was added diisobutylaluminum hydride (17 mmol, 17 ml of 1M hexane solution) at -78°C. After the stirring had been continued at the same temperature for 40 min, the mixture was decomposed with 5 % H_2SO_4 (50 ml) and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. A mixture of the remaining residue and formic acid (15 ml) was stirred at room temperature for 14 h. The mixture was made basic with 28 % ammonia and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The remaining residue was chromatographed on silica gel (25 g).

5: This compound was obtained by elution with $CHCl_3$ as an oil in 53 % yield, m/e 366 (M^+), ^1H NMR ($CDCl_3$) δ 1.08 (3H, d, J=7 Hz), 2.02-2.36 (1H, m), 2.53-3.58 (5H, m), 3.99-4.30 (1H, m), 4.42-4.70 (3H, m, $NCH_2C_6H_5$ and 11b-H), 6.70 (1H, s), 6.71 (1H, s), 7.10-7.33 (5H, m).

10a: This compound was obtained by elution with $CHCl_3$ as an oil in 48 % yield, m/e 428 (M^+), ^1H NMR ($CDCl_3$) δ 1.88-2.23 (1H, m), 2.39-2.60 (1H, m), 2.97 (1H, d,d, J=10.5 and 13.5 Hz), 3.19-3.48 (2H, m), 3.63 (3H, s), 3.89 (3H, s), 4.22 (1H, d,d, J=5 and 12 Hz), 4.62 (1H, d, J=15 Hz), 4.73 (1H, d, J=15 Hz), 4.89 (1H, d,d, J=5 and 13.5 Hz), 6.40 (1H, s), 6.72 (1H, s), 7.22-7.50 (10H, m). Signal due to 7-H is concealed beneath CH_3O signal.

10b and 11a: Elution with AcOEt-hexane (1:2, v/v) gave 11a as an oil in 34 % yield, m/e 442 (M^+-46), ^1H NMR ($CDCl_3$) δ 0.89 (3H, d, J=7 Hz), 1.98-2.27 (1H, m), 2.85-3.45 (2H, m), 3.80 (3H, s), 3.87 (3H, s), 3.74-3.86 (2H, m), 4.03-4.11 (1H, m), 4.33 (2H, broad s), 4.58-4.84 (1H, m), 6.75-6.78 (3H, m), 7.00-7.42 (10H, m), 8.04 (1H, s). Successive elution with $CHCl_3$ gave 10b as an oil in 28 % yield, m/e 442 (M^+), ^1H NMR ($CDCl_3$) δ 1.23 (3H, d, J=7 Hz), 2.33-2.60 (1H, m), 2.77-3.29 (2H, m), 2.98 (1H, d,d, J=1 and 10.5 Hz, ax. 6-H), 3.61 (3H, s), 3.86 (3H, s), 4.37 (1H, d, J=15 Hz), 4.77 (1H, d, J=15 Hz), 4.81 (1H, d,d, J=5 and 13.5 Hz, eq. 6-H), 6.40 (1H, s), 6.77 (1H, s), 7.00 (10H, broad s). Signal due to 7-H and 11b-H are concealed beneath other signals.

10c and 11b: Elution with AcOEt-hexane (1:2, v/v) gave 11b as an oil in 30 % yield, m/e 502 (M^+-46), ^1H NMR ($CDCl_3$) δ 0.89 (3H, d, J=7 Hz), 2.06-2.26 (1H, m), 2.86-3.30 (2H, m), 3.66-3.86 (2H, m), 3.81 (6H, s), 3.86 (6H, s), 3.97-4.09 (1H, m), 4.33 (2H, broad s), 4.59-4.82 (1H, m),

6.76-6.83 (6H, m), 6.99-7.36 (5H, m), 8.07 (1H, s). Successive elution with $CHCl_3$ yielded 10c as an oil in 25 % yield, m/e 502 (M^+), ^1H NMR ($CDCl_3$) δ 1.22 (3H, d, J=7 Hz), 2.17-2.63 (1H, m), 2.78-3.30 (2H, m), 2.98 (1H, d,d, J=10.5 and 13.5 Hz, ax. 6-H), 3.67 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 4.39 (1H, d, J=15 Hz), 4.78 (1H, d,d, J=5 and 13.5 Hz, eq. 6-H), 4.80 (1H, d, J=15 Hz), 6.46 (1H, s), 6.83 (1H, s), 6.71-6.80 (3H, m), 7.34 (5H, broad s). Signals due to 7-H and 11b-H are concealed beneath other signals.

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