Synthesis of Some Azeto[2,1-*a*]isoquinolin-2-ones

Su-Dong Cho, Sung-Kyu Kim and Yong-Jin Yoon*

Department of Chemistry and Research Institute of Natural Sciences,
Gyeongsang National University, Chinju 660-701, Korea

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Some azeto[2,1-*a*]isoquinolin-2-ones were synthesized from 2-(3,4-dimethoxyphenyl)ethylamine in three steps in good yield.

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In previous paper [1], we reported the pharmacological characterization of effects of verapamil and 1-(4'-methoxybenzyl)-6,7-dihydroxy-3,4-dihydroisoquinoline on isolated guinea pig and rat trachesalis. Continuing the study on the pharmacological characterization of novel isoquinoline derivatives, we required azeto[2,1-*a*]-isoquinolines containing chlorine atoms at the C-1 position and/or at the C-1' position.

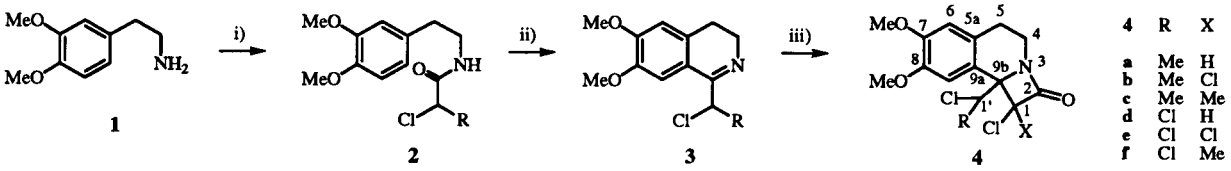
There have been reports on the synthesis of β-lactams from an imine and an α-substituted alkanoyl chloride in the presence of triethylamine [2-7]. The mechanism of this reaction involves an addition of an imine with a ketene that is prepared from an α-substituted alkanoyl chloride and triethylamine [3,4]. The synthesis of some azeto[2,1-*a*]-isoquinolines was also reported [2,8]. Therefore, we selected 6,7-dimethoxy-1-(chloroalkyl)-3,4-dihydroisoquinoline **3** as the starting material for the synthesis of isoquinoline β-lactams.

In this paper, we would like to report the synthesis of azeto[2,1-*a*]isoquinolin-2-ones **4** from 2-(3,4-dimethoxyphenyl)ethylamine **1** in three steps.

The reaction of 2-(3,4-dimethoxyphenyl)ethylamine (**1**) with an α-chloroalkanoyl chloride such as chloroacetyl chloride, 2,2-dichloroacetyl chloride or 2-chloropropionyl chloride and potassium carbonate in dichloromethane gave compounds **2** in excellent yields. The structures of compounds **2** were established by ir, ^{1}H nmr and elemental analyses. The infrared spectra of compounds **2** show the absorption peak of the amide carbonyl in the 1646-1676 cm^{-1} range and the absorption peak of the N-H in the 3206-3312 cm^{-1} range. The ^{1}H nmr spectra of compounds **2** showed proton signals for two OCH_3, two CH_2 and one NH (except for **2c**) involving aromatic, methyne and methyl protons. Compounds **2** are useful intermediates for the synthesis of various isoquinolines such as an isoquinonline containing a β-lactam or a pyridazino[1,4]oxazine ring [9].

The Bischler-Napieralski cyclization [10] of compounds **2** with phosphorus oxychloride gave the corresponding 3,4-dihydroisoquinoline derivatives **3** in good yields. The structures of compounds **3** were established by ir, ^{1}H nmr and elemental analyses. The infrared spectra of **3** did not indicate the presence of absorption peaks of the amide carbonyl group (1646-1676 cm^{-1}) or the N-H bond absorptions (3206-3312 cm^{-1}). The ^{1}H nmr spectra of **3** also showed the proton signals of two CH_2, two OCH_3 and two aromatic protons involving the signals of methyne and methyl protons, whereas the NH proton signal was not detected.

Scheme I



1 **2** **3** **4**

4	R	X
a	Me	H
b	Me	Cl
c	Me	Me
d	Cl	H
e	Cl	Cl
f	Cl	Me

i) RClHCCOCl, K_2CO_3, CH_2Cl_2, reflux, ii) $POCl_3$, reflux, iii) XClHCCOCl, $(Et)_3N$, dry CH_2Cl_2, 0° to room temperature

The reaction of 3,4-dihydroisoquinoline derivatives **3** with α-chloroalkanoyl chlorides in the presence of triethylamine in dry dichloromethane afforded the corresponding azeto[2,1-*a*]isoquinolin-2-ones **4** in 76-83% yields. The structures of compounds **4** were established by ir, nmr and elemental analyses. The infrared spectra of compounds **4** showed a new absorption peak of the β-lactam carbonyl at 1698-1660 cm^{-1}. The ^{1}H and ^{13}C nmr spectral data of compounds **4** were interpreted according to Bernath's data [8]. Nuclear magnetic resonance spectral data proving the suggested structures of **4** are listed in Tables 3 and 4. The ^{1}H nmr spectra of **4a-4d** showed proton signals of two diastereomers. However, we detected carbon signals for only one isomer in the ^{13}C nmr spectra for **4a-4d**. We also could not isolate each isomer. Two isomers for **4a-4d** may be due to the different conformations of the hydrogen atom (or the methyl group) at C-1 and the alkyl group at C-9b [8]. Proton signals of one isomer at C-1 and C-1' showed a relatively more upfield shift than the other

Table 1

Yields, Melting Points and Spectral Data of Compounds **2** and **3**

Compound No.	Yield (%)	mp(°C) [a]	IR (potassium bromide) (cm^{-1})	^1H NMR Solvent [b]	^1H NMR δ (ppm) [c]
2a	96	105-106	3250, 3100, 3024, 2957, 1676, 1594, 1522, 1461, 1344, 1270, 1249, 1222, 1164, 1132, 944, 860, 818	D	2.69 (t, 2H), 3.34 (q, 2H), 3.71 (s, OMe), 3.74 (s, OMe) 6.43 (s, 1H), 6.79 (m, Ar, 3H), 8.60 (t, NH)
2b	95	73-74	3312, 3064, 2938, 2952, 1646, 1550, 1520, 1262, 1230, 1140, 1026, 847, 810	D	1.50 (d, 3H, J = 9.3), 2.67 (t, 2H), 3.29 (q, 2H), 3.71 (s, OMe), 3.74 (s, OMe), 4.46 (q, 1H), 6.78 (m, Ar, 3H), 8.28 (t, NH)
2c	97	89-90	3206, 3112, 3026, 2992, 2956, 1654, 1590, 1528, 1344, 1276, 1250, 1234, 1170, 1147, 1048, 1032, 870, 819	D	2.80 (t, 2H), 3.54 (q, 2H), 3.86 (s, OMe), 3.87 (s, OMe), 4.02 (s, 2H), 6.79 (m, Ar, 3H), NH No detection
3a	93	89-90	3009, 2984, 2852, 1620, 1548, 1511, 1465, 1363, 1256, 1227, 1150, 1096, 1020, 860, 832	C	2.70 (t, 2H), 3.78 (t, 2H), 3.91 (s, OMe), 3.93 (s, OMe) 6.54 (s, 1H), 6.73 (s, Ar, 1H), 7.60 (s, Ar, 1H)
3b	87	105-106	3018, 2970, 2850, 1614, 1576, 1521, 1468, 1374, 1280, 1221, 1155, 1104, 1022, 870, 810	D	1.69 (d, 3H, J = 9.0), 2.59 (q, 2H), 3.47 (m, 2H), 3.79 (s, OMe), 3.81 (s, OMe), 5.59 (q, 1H), 6.90 (s, Ar, 1H), 7.27 (s, Ar, 1H)

[a] Recrystallization solvent for all compounds; diethyl ether/*n*-hexane (1:1, v/v). [b] Solvents: D = dimethyl-d_6 sulfoxide, C = deuteriochloroform. [c] Abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, Ar = Aromatic. Coupling constant (J) in Hertz. All NH proton signals were exchangeable with deuterium oxide.

Table 2

Yields, Melting Points and Infrared Spectral Data of Compound **4**

Compound No.	Yield (%)	mp (°C) [a]	IR (potassium bromide) (cm^{-1})
4a	76	132-133 (EH)	3012, 2954, 2840, 1680, 1608, 1515, 1450, 1394, 1270, 1234, 1210, 1134, 1092, 1020, 866, 780, 752
4b	82	105-106 (EH)	3006, 2976, 2824, 1664, 1604, 1510, 1420, 1328, 1264, 1204, 1122, 1034, 980, 912, 860
4c	76	99-100 (EH)	3004, 2948, 2922, 2836, 1670, 1640, 1608, 1516, 1462, 1410, 1354, 1336, 1270, 1254, 1210, 1140, 1102, 1020, 898, 872, 840, 782, 750
4d	72	158-159 (E)	3018, 2974, 1692, 1520, 1390, 1276, 1238, 1214, 1112, 1038, 916, 580
4e	83	133-134 (E)	3014, 2970, 2940, 2824, 1660, 1618, 1525, 1404, 1356, 1290, 1204, 1128, 1038, 987, 923, 880
4f	82	144-145 (EH)	3042, 2960, 2934, 2854, 1698, 1522, 1478, 1412, 1332, 1280, 1238, 1222, 1140, 1100, 1022, 966, 876, 800, 640

[a] Recrystallization solvent; EH = diethyl ether/*n*-hexane (1:1, v/v). E = diethyl ether.

Table 3

^1H NMR Spectral Data of Compound **4** [a]

Compound No	Solvent [b]	C-1 1H (s)	C-1 CH_3 (s)	C-1' 1H (m)	C-1' CH_3 (s)	C-4 2H [c] (a/e)	C-5 2H [c] (a/e) (m)	C-6 1H (s) (m)	C-9 1H (s)	C-7 OCH_3 (s)	C-8 OCH_3 (s)
4a	C	4.16 [d]	4.16 [d]	2.44	3.38 3.45	2.75 2.80	6.68	6.81	3.86	3.88	
		4.24 [d]	4.24 [d]	2.46	4.43 4.49	3.00 3.06					
	(m)										
4b	C		4.63	1.63	3.24 3.38	2.68 2.76	6.59	7.38	3.83	3.84	
			4.76	1.65	4.51 4.59	3.00 3.11					

Table 3 (continued)

Compound No	Solvent [b]	C-1 1H (s)	C-1 CH_3 (s)	C-1' 1H (m)	C-1' CH_3 (s)	C-4 2H [c] (a/e)	C-5 2H [c] (a/e) (m)	C-6 1H (s) (m)	C-9 1H (s)	C-7 OCH_3 (s)	C-8 OCH_3 (s)
4c	D		2.47	4.73	1.67	3.38	2.72	6.67	6.84	3.88	3.88
					3.48	2.82					
			4.85	1.69	4.36	2.98					
					4.44	3.08					
4d	C	4.08	4.54		3.26	2.67	6.60	7.41	3.83	3.83	
					3.36	2.76					
		4.20	4.61		4.08	2.99					
					4.20	3.11					
4e	C			6.35	3.57	2.81	6.66	7.44	3.90	3.94	
					3.69	2.90					
					4.02	3.02					
					4.10	3.14					
4f	C		2.43	6.38	3.37	2.69	6.62	6.75	3.81	3.81	
					3.46	2.78					
					4.32	2.95					
					4.40	3.05					

[a] Abbreviations used: *s* = singlet, d=doublet, m = multiplet, a = axial, e = equatorial. [b] Solvent: C = deuteriochloroform, D = dimethyl-d_6 sulfoxide. Chemical shift (δ) in ppm unit. [c] Assignment may be interchanged. [d] The protons at C-1 and C-1' show same chemical shift.

Table 4

^{13}C NMR Spectral Data of Compound **4**

Compound No. Solvent [a]	**4a** C	**4b** C	**4c** D	**4d** C	**4e** C	**4f** C
C-1'	110.9	110.4	50.2	110.1	75.8	110.1
C-1	112.1	110.9	110.8	111.1	87.0	111.1
C-2 (C=O)	166.2	168.0	167.6	165.1	161.4	162.7
C-4	43.0	43.1	42.7	41.9	36.6	43.7
C-5	27.9	27.1	26.5	27.1	26.1	26.9
C-5a	133.1	134.6	131.9	134.0	128.2	131.8
C-6[b]	125.1	119.3	111.8	119.7	111.6	124.1
C-9[b]	129.1	122.8	124.5	122.4	112.2	128.4
C-9a	129.7	128.9	128.3	129.0	118.6	128.8
C-7[b]	147.5	146.5	146.3	146.5	148.8	146.7
C-8[b]	150.2	149.8	149.0	150.0	150.1	149.4
C-9b	43.9	49.6	42.7	43.1	72.1	64.6
OMe (C-7)[b]	56.7	55.8	55.5	55.8	55.7	55.8
OMe (C-8)[b]	56.9	56.1	55.9	56.0	56.0	56.1
CH_3 (C-1)	—	—	23.3	—	—	23.4
CH_3 (C-1')	24.3	20.4	20.6	—	—	—

[a] C = Deuteriochloroform, D = dimethyl-d_6 sulfoxide. [b] Assignment may be interchanged.

Table 5

Elemental Analytical Data of Compound **2**, **3** and **4**

Compound No	Molecular Formula	Calcd./Found (%) C	H	N
2a	$C_{12}H_{15}NO_3Cl_2$	49.33	5.17	4.79
		49.56	5.35	4.99
2b	$C_{13}H_{18}N0_3Cl$	57.46	6.68	5.15
		57.76	6.90	5.35
2c	$C_{12}H_{16}NO_3Cl$	55.93	6.26	5.43
		55.99	6.55	5.76
3a	$C_{12}H_{13}NO_2Cl_2$	52.57	4.78	5.11
		52.75	4.88	5.36
3b	$C_{13}H_{16}NO_2Cl$	61.54	6.36	5.52
		61.71	6.52	5.60
4a	$C_{15}H_{17}NO_3Cl_2$	54.56	5.19	4.24
		54.88	5.34	4.54
4b	$C_{15}H_{16}NO_3Cl_3$	49.41	4.42	3.84
		49.70	4.64	3.97
4c	$C_{16}H_{19}NO_3Cl_2$	55.83	5.56	4.07
		55.95	5.81	4.15
4d	$C_{14}H_{14}NO_3Cl_3$	47.96	4.02	3.99
		48.01	4.14	4.04
4e	$C_{14}H_{13}NO_3Cl_4$	43.67	3.40	3.64
		43.98	3.66	3.78
4f	$C_{15}H_{17}NO_3Cl_2$	54.56	5.19	4.24
		54.55	5.56	4.53

isomer. The signals of the axial and the equatorial protons at C-4 and C-5 for **4** also detected as multiplets, respectively. The ^{13}C nmr spectra of compounds **4** show carbon signals at C-1 (δ 110.8-112.1 ppm except for **4e** at δ 87.0 ppm), carbonyl (C-2) (δ 161.4-168.0 ppm), C-4 (δ 36.6-43.7 ppm), C-5 (δ 26.1-27.9 ppm) and C-9b (δ 42.7-64.6 ppm except for **4e** at δ 72.1 ppm) involving aromatic and other carbon signals.

Further work including the pharmacological action, the separation of isomers, the study on nuclear magnetic resonance, X-ray diffraction of pure isomers and additional chemical transformations for compounds **4** are under way in our laboratory.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 spectrometer with chemical

shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C instrument. Open-bed column chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-chloroacetamide (**2a**), *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2,2-dichloroacetamide (**2b**) and *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-chloropropanamide (**2c**).

A mixture of 2-(3,4-dimethoxyphenyl)ethylamine (**1**, 0.276 mole), α-chloroalkanoyl chloride derivatives (0.276 mole), anhydrous potassium carbonate (0.277 mole) and dichloromethane (300 ml) was refluxed for 2 hours. After cooling to room temperature, the reaction mixture was filtered and washed with dichloromethane (150 ml x 2). The solvent of the combined solutions was evaporated under reduced pressure. The residue was dissolved in water/diethyl ether (1:1, v/v, 100 ml) with stirring. The resulting solid was filtered and washed with diethyl ether (20 ml). Recrystallization of the crude product from diethyl ether/*n*-hexane (1:1, v/v) yielded compound **2a, 2b** and **2c** as white crystals, respectively.

6,7-Dimethoxy-1-chloroalkyl-3,4-dihydroisoquinolines **3a** and **3b**.

A solution of **2b** or **2c** (0.02 mole), toluene (80 ml) and phosphorus oxychloride (0.022 mole) was refluxed for 4 hours. After cooling to room temperature, the solution was evaporated under reduced pressure. The residue was poured into aqueous ammonia (28%, 50 ml) with stirring. The resulting solid was filtered and washed with *n*-hexane (10 ml x 2). The crude product was applied to the top of an open-bed silica gel column (10 x 3 cm). The column was eluted with dichloromethane/ethyl acetate (10:3, v/v). The fractions containing the product were combined and evaporated under reduced pressure. Recrystallization of the crude product from diethyl ether/*n*-hexane (1:1, v/v) gave compound **3a** or **3b**.

Azeto[2,1-*a*]isoquinolines **4**.

A mixture of the specific acid chloride (0.042 mole), dry dichloromethane (100 ml) and triethylamine (0.043 mole) was stirred for 10 minutes at 0°. The solution of the specific compound **3** (0.02 mole) dissolved in dry dichloromethane was added slowly to the reaction mixture at 0°. The reaction mixture was stirred for 2 hours at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether (50 ml). The solution was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (10 x 3 cm). The column was eluted with dichloromethane/ethyl acetate (10:1, v/v). Fractions containing the requisite product were combined and were evaporated under reduced pressure. Recrystallization of the crude product from diethyl ether for compounds **4d** and **4e** or diethyl ether/*n*-hexane **4a, 4b, 4c** and **4f** yielded compounds **4**.

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