http://dx.doi.org/10.5012/bkcs.2012.33.1.341

Synthesis of *N*-Aryl-4,5,6,7-tetrahydroindoles

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Received November 7, 2011, Accepted November 21, 2011

Key Words : Tetrahydroindole, Tetrahydro-4-oxoindole, Indole

Indole, unlike pyrrole, undergoes electrophilic substitution at C-3. For example, a Vilsmeier reaction of indole gives 3-formylindole exclusively.[1] On the other hand, the same reaction with pyrrole produces 2-formylpyrrole.[2] If the introduction of a nucleophile at the C-2 of indole is desired, 4,5,6,7-tetrahydroindole should be employed as a starting material. An introduction of the substitution and a subsequent dehydrogenation of the tetrahydroindole should be carried out to complete the synthesis of the 2-substituted indole. For such purpose we previously reported the synthesis of 5-substituted 4,5,6,7-tetrahydroindoles from cyclohexanones with suitable substituents at 4-position of the cyclic ketone.[3]

As an extension of such a synthesis, we were interested in the preparation of *N*-aryl-4,5,6,7-tetrahydroindoles. One way of introducing the aryl group is to apply C-N bond formation reaction, which has been an active research area in the past decade. Numerous reports can be found in literature on the *N*-arylation of indole.[4] However, there are a few reports on the direct arylation of 4,5,6,7-tetrahydroindoles. Bekolo reported the *N*-arylation of 4,5,6,7-tetrahydro-4-oxoindole (**3**) to prepare the *N*-aryl-4,5,6,7-tetrahydro-4-oxoindole (**5**) by the cross coupling of arylboronic acids, *p*-Z-C_6H_4-$B(OH)_2$ (Z = H, *o*-Me, *p*-*t*-Bu, *p*-OEt, *p*-Cl) in the presence of $Cu(OAc)_2$ and ethyl diisopropylamine in dichloromethane solution at room temperature.[5] But the yields were in the range of 43-70% after 6-14 days of reaction time. Nishio, et. al. prepared *N*-aryl-4,5,6,7-tetrahydroindoles (**6f**, **6g**, **6h**, **6i**) from 1-aryl-1,4,5,6,7,7a-hexahydro-2*H*-indol-2-ones by using Lawesson's reagent [2,4-bis-(*p*-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] in 27-55% yields.[6] Olesen *et al*. reported the preparation of **6f**, **6g**, and **6i** by the reactions of the corresponding cyclohexanone imines with 2-chloroacrylonitrile in 25-61% yields.[7]

Obviously, direct arylation of the tetrahydroindole (**4**) to synthesize the *N*-aryltetrahydroindole (**6**) requires a decent method for the preparation of **4**. There are several reports for such preparations using cyclohexanone as starting material. It was converted to a dimethylhydrazone which was reacted with *n*-BuLi to give 1-dimethylamino-4,5,6,7-tetrahydroindole, but the removal of the dimethylamino group was not efficient.[8] Alternatively, cyclohexanone was converted to an oxime, which was reacted with acetylene in KOH and DMSO.[9] But the method suffers the disadvantage of the formation of *N*-vinyl derivatives of **4**. An oxime prepared from *O*-(2-hydroxyethyl)hydroxylamine could be converted to **4**[10] upon the exchange of the –OH with iodine and subsequent cyclization by *t*-BuOK in *t*-BuOH in good yield.

Tetrahydroindole (**4**) itself is very unstable, requiring storage in a freezer under N_2.[3] Furthermore, C-N bond formation is an additional step which requires the use of a transition metal catalyst. Therefore, a shorter procedure in which the *N*-aryl group was introduced in the earlier step is desirable. Here we report a three-step preparation of *N*-aryl-4,5,6,7-tetrahydroindoles (**6**) from cyclohexane-1,3-dione (**1**).

There are two reports of employing **1** for similar purpose. Martifnez *et al*. treated **1** with chloroacetone to prepare 2-(2-oxo-1-propyl)-1,3-cyclohexanedione, which was converted to 2-methyl derivatives of **5**.[11] Piras *et al*. reacted **1** with ethyl bromopyruvate in the presence of EtOH/KOH under reflux conditions to prepare 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid, and then converted to **5a** and **5g** by heating with aniline and *p*-methoxyaniline, respectively, in 75% yield.[12]

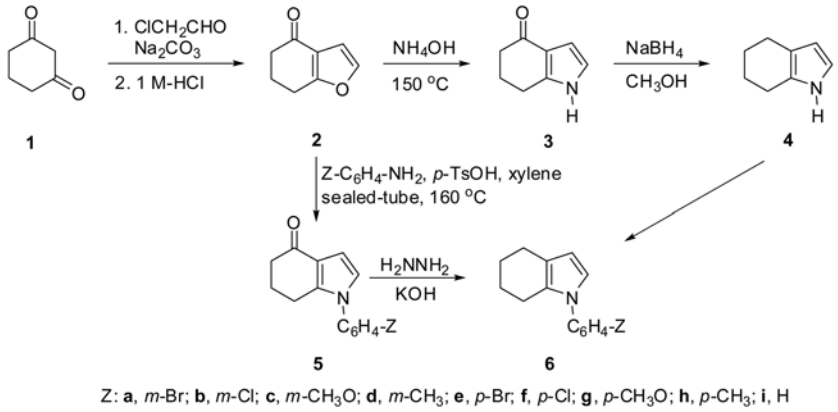
Results and Discussion

Scheme 1 shows the synthetic procedure employed in the present research.

The key intermediate, 4,5,6,7-tetrahydro-4-oxobenzofuran (**2**) was prepared from **1** and chloroacetaldehyde.[13] Conversion of **2** to **3** was typically carried out by heating with 28%-NH_4OH in a sealed tube at 150 °C for 12 h. However, various conditions tried for the conversion of **2** to *N*-aryl derivatives **5** were unsuccessful. The best conditions turned out to be heating a mixture of **2** and arylamines (1:5 by mole) placed in a stainless sealed tube together with xylene and a catalytic amount of *p*-TsOH at 160 °C for 24 h. The method seems to be better because of simplicity and good yields after purification ranging 59-95%. The yields and mp of **5** and **6** are listed in Table 1.

Reduction of the carbonyl group of **5** to the methylene of **6** was accomplished by Wolff-Kishner procedure using hydrazine hydrate. However, the purification by column chromatography was troublesome, and the yields were low due to the change of **6** in air.

The structures of **5** were readily confirmed by spectroscopic methods. The ^1H and ^{13}C NMR data are listed in Tables 2 and 3, respectively. In addition to the carbonyl



Scheme 1

Table 1. Yields and mp of **5** and **6**

Compound	**5**		**6**	
	Yield, %	mp	Yield, %	mp
a	59	121	40	liquid
b	69	112	39	liquid
c	83	129	13	liquid
d	80	131	25	liquid
e	76	135	61	liquid
f	71	122	50	liquid
g	95	149	18	liquid
h	88	114	50	liquid
i	81	102	62	liquid

stretching at around 1700 cm^{-1} of their IR spectra, two triplets at about δ 2.52 (5-H) and 2.76 (7-H) with *J* values of 5-6 Hz and a multiplet at about δ 2.13 (6-H) with similar coupling constants in their ^{1}H-NMR spectra indicate the 4,5,6,7-tetrahydro-4-oxoindole skeleton. The 2- and 3-pyrrolyl protons are apparent at δ 6.79 and 6.70 as each doublet, respectively, with coupling constants of ~3 Hz.

On the other hand, ^{1}H-NMR spectra of **6** show a multiplet at about δ 1.78 (5- and 6-H) and a set of two apparent singlets at about 2.55 and 2.59 (4- and 7-H). The 2- and 3-pyrrolyl protons in **6** show signals at about δ 6.75 and 6.10, respectively. Contrasting to the small changes in the chemical shifts of 5-, 6-, and 7-Hs between **5** and **6**, the signals corresponding to the 3-H in **6** shift upfield significantly. But, ^{13}C chemical shifts show the opposite trend, an upfield shift for 2-C (about 123 ppm to 120 ppm) and a downfield shift for 3-C (about 106 ppm to 108 ppm) depending on the presence of the carbonyl group in **5** or the absence in **6**. The observations are consistent with the diamagnetic isotropic effect of the carbonyl group.

In summary, *N*-aryl-4,5,6,7-tetrahydroindoles were prepared in moderate to good yields from cyclohexane-1,3-

Table 2. ^{1}H Chemical Shift Values of 4-Oxotetrahydroindoles (**5**) and Tetrahydroindoles (**6**) in chloroform-*d* (0.1 M)

	2-H	3-H	4-H	5-H	6-H	7-H	2'-H	3'-H	4'-H	5'-H	6'-H
5a	6.79	6.70		2.52	2.14	2.78	7.50		7.55	7.37	7.27
6a	6.74	6.10	2.57	1.79	1.79	2.58	7.47		7.41	7.05	7.24
5b	6.79	6.70		2.53	2.14	2.79	7.34		7.39	7.43	7.23
6b	6.74	6.10	2.57	1.78	1.78	2.58	7.30		7.25	7.33	7.19
5c	6.80	6.68		2.52	2.12	2.79	6.84		6.94	7.38	6.92
6c	6.77	6.09	2.59	1.79	1.79	2.60	6.85		6.89	7.31	6.83
5d	6.79	6.68		2.52	2.12	2.77	7.12		7.22	7.36	7.11
6d	6.75	6.08	2.56	1.78	1.78	2.59	7.10		7.10	7.28	7.10
5e	6.77	6.70		2.52	2.13	2.76	7.21	7.62		7.62	7.21
6e	6.72	6.10	2.54	1.78	1.78	2.58	7.17	7.52		7.52	7.17
5f	6.77	6.69		2.52	2.13	2.75	7.27	7.47		7.47	7.21
6f	6.72	6.10	2.54	1.78	1.78	2.58	7.23	7.37		7.37	7.23
5g	6.74	6.66		2.51	2.12	2.72	7.23	6.99		6.99	7.23
6g	6.70	6.07	2.50	1.77	1.77	2.59	7.21	6.93		6.93	7.21
5h	6.77	6.68		2.51	2.12	2.75	7.20	7.28		7.28	7.20
6h	6.74	6.08	2.55	1.78	1.78	2.60	7.18	7.21		7.21	7.18
5i	6.81	6.70		2.52	2.13	2.78	7.32	7.49	7.41	7.49	7.32
6i	6.78	6.11	2.58	1.79	1.79	2.61	7.31	7.42	7.28	7.42	7.31

Table 3. ^{13}C Chemical Shift Values of the 4-Oxotetrahydroindoles (**5**) and Tetrahydroindoles (**6**) in chloroform-*d* (0.1 M)

	2-C	3-C	3a-C	4-C	5-C	6-C	7-C	7a-C
5a	122.90	106.87	122.17	194.52	37.73	23.97	23.04	143.19
6a	119.68	108.77	119.63	23.45	23.28	23.21	23.55	127.99
5b	122.88	106.85	122.17	194.52	37.73	23.97	23.06	143.15
6b	119.68	108.75	119.63	23.48	23.28	23.22	23.55	127.99
5c	123.05	106.33	121.81	194.59	37.78	24.00	23.10	143.31
6c	119.81	108.08	119.07	23.52	23.38	23.26	23.60	128.06
5d	123.12	106.22	121.71	194.63	37.80	24.02	23.06	143.36
6d	119.82	107.90	118.86	23.44	23.44	23.27	23.61	128.05
5e	122.87	106.78	122.10	194.50	37.72	23.96	23.00	143.12
6e	119.64	108.61	119.48	23.41	23.29	23.21	23.55	127.97
5f	122.92	106.73	122.07	194.45	37.72	23.95	22.97	143.16
6f	119.70	108.52	119.42	23.38	23.30	23.21	23.54	128.02
5g	123.37	105.98	121.43	194.57	37.78	23.95	22.81	143.64
6g	119.99	107.50	118.38	23.46	23.24	23.12	23.56	128.02
5h	123.17	106.15	121.63	194.61	37.79	23.99	22.97	143.42
6h	119.85	107.75	118.70	23.44	23.33	23.27	23.60	128.11
5i	123.10	106.37	121.81	194.64	37.79	24.01	23.05	143.35
6i	119.80	108.06	118.97	23.43	23.39	23.25	23.59	128.06

dione in three steps.

Experimental Section

Nuclear magnetic resonance (NMR) spectra in chloroform-*d* solution were recorded on a Bruker DPX-400 FT NMR spectrometer in the Central Lab of Kangwon National University at 400 MHz for ^{1}H and 100 MHz for ^{13}C and were referenced to tetramethylsilane. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer.

Cyclohexane-1,3-dione, chloroacetaldehyde, and arylamines were obtained as the commercial products and used as delivered. Column chromatography was performed using silica gel and 1:1 mixture of ethyl acetate and hexane as elution solvent.

Preparation of 1-Aryl-4,5,6,7-tetrahydro-4-oxoindoles. An Illustrative Procedure with 5i. In a stainless steel tube (volume 42 mL) were placed 4,5,6,7-tetrahydro-4-oxobenzofuran[13] (2.04 g, 15.0 mmoles), aniline (6.98 g, 75.0 mmoles), *p*-xylene (14 mL), and *p*-TsOH (a few granules). The tube was sealed and placed in an oil bath at 160 °C for 24 h. After cooling to room temperature, the solution was brought to pH 1 by addition of 1 *M*-HCl. The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. After removal of the drying agent and the solvent, the residue was recrystallized from ethanol.

Preparation of 1-Aryl-4,5,6,7-tetrahydroindoles. An Illustrative Procedure with 6i. A mixture of **5i** (2.11 g, 10.0 mmoles), hydrazine hydrate (1.45 mL, 30.0 mmoles), and KOH (1.68 g, 30.0 mmoles) in ethylene glycol (20 mL) were heated at reflux for 5 h. After cooling to room temperature, water (100 mL) was added and the pH of the mixture was adjusted to 1 by adding 1 M-HCl (ca. 40 mL). Toluene (50 mL) was added and the mixture was left at room temperature for 5 h. The mixture was extracted with CH_2Cl_2 (80 mL × 4). The organic extract was dried over $MgSO_4$ and then the solvent was removed by evaporation under aspirator pressure. The resulting liquid was purified by chromatography (silica gel, hexane-EtOAc 7:3).

Acknowledgments. We thank Dr. Gary Kwong for proofreading the manuscript.

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