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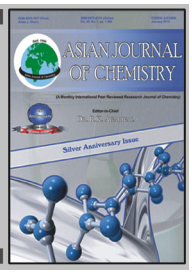

Synthesis of Heteroaromatic Derivatives with Nitrogen Atoms: Tripyrrolyl Pyrimidine and Tripyrrolyl[1,3,5]triazine

D.H. LEE[1], S.G. LEE[1], D.I. JUNG[1,*] and J.T. HAHN[2]

[1]Department of Chemistry, Dong-A University, Busan 604714, South Korea
[2]Department of Beautycare, Youngdong University, Youngdong 370701, South Korea

*Corresponding author: Fax: +82 51 2007249; Tel: +82 51 2007249; E-mail : dijung@dau.ac.kr

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As a part of a research program related to the synthetic study of pharmacologically and photoconductively interesting pyrrole derivatives, we have synthesized 1-arylpyrroles (**3a-e**), 9-arylcarbazoles (**4a-e**), aminophenylpyrroles (**6a**,**b**), dipyrrolylbenzenes (**7a-c**), 2,4,6-*tri*-pyrrol-1-yl-pyrimidine (**8**) and 2,4,6-*tri*-pyrrol-1-yl[1,3,5]triazine (**9**). We proposed a plausible mechanism for the formation of 9-arylcarbazole.

Key Words: Arylpyrroles, Arylcarbazoles, Diphenylbenzenes, Tripyrrolylpyrimidine, Tripyrrolyl[1,3,5]triazine.

INTRODUCTION

Nitrogen containing heterocycles, such as pyrroles and carbazoles have attracted considerable attention due to their numerous applications in pharmaceutical and synthetic chemistry[1]. These heterocyclic moieties are also found in a variety of biologically active synthetic and natural products[2]. Although many efficient processes had already been reported, but, the development of new methods is still in demand[3]. Most methods involve two or more steps to synthesize these heterocycles resulting in 2,3-di- or polysubstituted products[4]. Ideally the synthesis of these heterocycles would involve only one step, directly from simple, readily available substrates. Although, a similar idea had been proposed earlier, it suffered serious drawbacks such as low yields (up to 50 %) and low selectivities[4,5]. In present study, we report a convenient one pot synthesis of *N*-pyrrolylbenzenes and carbazoles from commercially available aromatic amines using glacial acetic acid as an effective catalyst. In the course of the investigation for the synthesis of pyrrole derivatives (**3**), we have found the formation of 9-arylcarbazoles (**4**) under refluxing glacial acetic acid. Thus we report the results here. 1-Arylpyrroles were prepared by the previously published procedure[5].

EXPERIMENTAL

Melting points were determines on a Büchi 510 capillary melting point apparatus and uncorrected. Infrared spectra were recorded on a Perkin-Elmer 683 spectro-photometer. NMR spectra were recorded on a Varian XL-300 or Brüker AC 200 FT-NMR spectrometer in $CDCl_3$ containing Me_4Si as an internal reference. Mass spectra were obtained by using JEOL JMS DX 303 or HP 5892 Mass Spectrometer.

Preparation of 9-phenylcarbazole (4c) in glacial acetic acid: A mixture of **3c** (0.72 g, 5 mmol) and **2** (1.32 g, 10 mmol) in glacial acetic acid was refluxed for 19 h. Removal of the solvent under reduced but pressure followed by flash column chromatography on a silica-gel (*n*-hexane:ethyl acetate = 10:1, v/v) gave the desired 9-phenylcarbazole **4c** as a solid (0.67 g, 55 %); m.p. 94-96 ºC; IR (KBr, ν_{max}, cm^{-1}) 3050 (aromatic C-H) 1590, 1240, 760; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25-8.18 (m, 13H, phenyl or carbazolyl group); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 129.9, 127.5, 125.9, 120.3, 119.9, 109.8; Mass (m/e) 243 (M^+), 166, 140, 77.

Preparation of 9-(4'-methoxyphenyl)carbazole (4a) by direct and one-pot reaction in glacial acetic acid: A mixture of **1a** (1.85 g, 15 mmol) and **2** (6.20 g, 45 mmol) in glacial acetic acid was refluxed for 12 h. The solvent was removed under aspirator pressure and the remaining sticky oil was separated by flash column chromatography on a silica gel (*n*-hexane). Yield 1.23 g (30 %); IR (KBr, ν_{max}, cm^{-1}) 3070 (aromatic C-H) 2950, 1600, 1210, 1120, 800; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.66 (s, 3H, CH_3) 7.25-8.18 (m, 12H, phenyl and carbazolyl group); Mass (m/e) 273 (M^+), 258, 242, 166.

Physical data of 1-arylpyrroles: 1a ^1H NMR ($CDCl_3$, 200 MHz) δ 3.83 (s, 3H, CH_3), 6.32 (t, 2H), 6.92-6.99 (m, 2H), 7.28-7.33 (m, 2H); Mass (m/e) 173 (M^+). **1b** ^1H NMR ($CDCl_3$, 200 MHz) δ 6.41-6.44 (t, 2H), 7.16-7.18 (t, 2H), 7.49-7.54 (m, 2H), 8.28-8.33 (m, 2H). **1c** ^1H NMR ($CDCl_3$, 200 MHz) δ 6.33-6.35 (t, 2H), 7.08-7.10 (t, 2H), 7.23-7.24 (m, 1H), 7.39-7.42 (m, 4H); Mass (m/e) 143 (M^+). **1d** Mass (m/e)

188 (M^+). **1e** Mass (m/e) 222 (M^+).

Physical data of 9-arylcarbazoles: 4a IR (KBr, ν_{max}, cm^{-1}) 3070-2980 w (aromatic C-H), 1600-1400s (aromatic C=C), 1120 s (C-O), 1210s (C-N), 800-650 w (=CH, aromatic OOP); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.83 (s, 3H, CH_3), 7.02-8.19 (m, 12H, phenyl and carbazolyl group); Mass (m/e): 274 (M^++1, 25), 273 (M^+, 100), 258, 242, 166. **4b** IR (neat) 3050-2900w (aromatic C-H), 1550s, 1390s (NO_2), 1500-1450s (aromatic C=C), 1230s (C-N), 760-720w (=CH. Aromatic OOP) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.34-7.68 (m, 12H, phenyl and carbazolyl group); Mass (m/e) 268 (M^+), 242, 166, 140, 46, 30. **4c** IR (KBr, ν_{max}, cm^{-1}) 3050-2950w (aromatic C-H), 1590s (aromatic C=C), 1240s (C-N), 760-700s (=CH aromatic OOP); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.20-8.18 (m, 13H, phenyl and carbazolyl group); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 129.89, 127.45, 125.91, 120.30, 119.89, 109.76; Mass (m/e): 244 (M^++1, 23), 243 (M^+, 100), 166, 140, 77. **4d** IR (neat) 3050-2900w (aromatic C-H), 1550s, 1390s (NO_2), 1500-1450s (aromatic C=C), 1230s (C-N), 760-720w (=CH, aromatic OOP) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.34-7.68 (m, phenyl and carbazolyl group); Mass (m/e): 288, 242, 166, 140, 46, 30. **4e** IR (neat) 3030-3010w (aromatic C-H), 1500-1450s (aromatic C=C), 1215s (C-N), 1005s (aryl-Br), 770-710s (=CH, aromatic OOP); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25-8.20 (m, 12H, phenyl and carbazolyl group); Mass (m/e): 323 (M^++2, 103), 321(M^+, 100), 241, 166, 140, 76.

1-(2-aminophe-nyl)pyrrole (6a): Yield : 73 %; m.p.: 102-103 ºC; R_f : 0.44 (TLC eluent; *n*-hexane : EtOAc = 20 : 1, v/v); ^1H NMR ($CDCl_3$, 200 MHz) : δ 3.68 (s, 2H), 6.31-6.35, (s, 2H), 6.72-6.78 (m, 2H), 6.79-6.82 (s, 4H), 7.10-7.15 (m, 2H); Mass (70eV), m/z : 158.

1,2-Dipyrrolylbenzene (7a): Isolated yield : 5 %; R_f: 0.68 (TLC eluent ; EtOAc : *n*-hexane = 1 : 20, v/v); Mass (70 eV), m/z (rel. Int. %) : 208 (19), 158 (62), 132 (71), 77 (71), 63 (90), 51 (100); ^1H NMR ($CDCl_3$, 200 MHz) : δ 7.62 (m, 2H), δ 7.58 (m, 2H), δ 7.26 (m, 4H) δ 6.41 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) : δ 143.7, 131.3, 131.0, 130.6, 129.4, 122.6, 120.4, 120.1, 110.5, 108.9, 48.9, 29.6; Anal. calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45; Found : C, 80.71; H, 5.80 ; N, 13.43.

1-(3-Aminophenyl)-pyrrole (6b): Yield: 28 %; m.p.: 120-122 ºC; R_f : 0.44 (TLC eluent; *n*-hexane : EtOAc = 20 : 1, v/v); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.20 (s, 2H), 6.20 (s, 2H), 7.10 (m, 2H), 7.30 (s, 2H); Mass (70 eV), m/z: 158.

1,3-Dipyrrolylbenzene (7b): Yield: 37 %; m.p.: 107-108 ºC; R_f : 0.675 (TLC eluent; *n*-hexane: EtOAc = 5 : 1, v/v); ^1H NMR ($CDCl_3$, 200 MHz): δ 6.36-6.38 (t, 4H), 7.10-7.12 (t, 4H), 7.25-7.29 (m, 3H), 7.41-7.60 (m, 1H) Mass (70eV), m/z: 208.

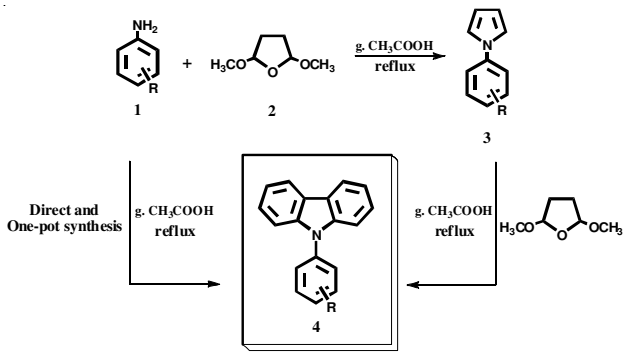
1,4-Dipyrrolyl-benzene (7c): Yield : 58 %; m.p. : 213-214 ºC; R_f : 0.44 (TLC eluent; *n*-hexane: EtOAc = 10 : 1, v/v); ^1H NMR ($CDCl_3$, 200 MHz): δ 6.17-6.22 (t, 4H), 6.89-6.96 (m, 4H), 7.16 (m, 2H), 7.36 (m, 2H); Mass (70 eV), m/z: 208.

2,4,6-Tripyrrol-1-yl-pyrimidine (8): Isolated yield: 30 % (39.5 %); m.p. : 171-173 ºC; R_f : 0.26 (TLC eluent; EtOAc: *n*-hexane = 1 : 40, v/v); Mass (70 eV), m/z (rel. Int. %): 275 (10), 51 (100), 129 (30), 75 (30), 102 (20); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.82-7.84 (t, 3H), 7.61-7.62 (t, 4H), 6.84 (s, 2H), 6.42-6.44 (t, 3H), 6.35-6.37 (t, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.1, 119.51,118.98, 118.50, 118.03, 114.44, 113.16, 112.74, 112.35, 111.88, 111.51, 88.23; Anal. calcd. for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44; Found: C, 69.78; H, 4.74, N, 25.41.

2,4,6-Tri-pyrrol-1-yl-[1,3,5]triazine (9): Isolated yield : 29 % (30 %); m.p.: 187-189 ºC; R_f : 0.35 (TLC eluent; $CHCl_3$: *n*-hexane = 1 : 40, v/v); Mass (70 eV), m/z (rel. Int. %): 276 (10), 51 (100), 129 (30), 75 (30), 102 (20); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.81-7.84 (t, 6H), 6.39-6.41 (t, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 182.21, 138.88, 138.36, 132.95, 132.41.

RESULTS AND DISCUSSION

Generarlly, synthetic methods of 1-arylpyrroles **3** from amines **1** and **2** have been known for a long time[8-11]. 1-Arylpyrroles **3** were obtained in quantitative yields by the general method (Table-1). The effect of organic dicarboxylic acids on the synthesis of **3** was investigated (Table-2). Among organic dicarboxylic acids, adipic acid gave the highest yield of **3c** (Table-2, Entry 1) (**Scheme-I**).



Scheme-I: Synthesis of 9-arylcarbazoles

The yield of **3c** was the lowest when acetonedicarboxylic acid was used (Table 2, Entry 3), but *N*-phenylnortropinone was formed as the major product in 48 % yield.

TABLE-1
PHYSICAL DATA OF 1-ARYLPYRROLES (**3**)

	R	Yield (%)[a]	m.p. (ºC)	Lit.[8] m.p. (ºC)
a	*p*-OCH_3	98	108-109	108
b	*p*-NO_2	88	180-181	180-181
c	H	98	58-59[6,7]	58-59
d	*m*-NO_2	87	81-82[7]	81-82
e	*m*-Br	93	64-65[6,7]	–

[a]Isolated yield

TABLE-2
YIELDS OF 1-PHENYLPYRROLE (**3c**) DEPENDING ON THE DICARBOXYLIC ACIDS

Entry	Organic dicarboxylic acid	Refiux (min)	Yield (%)[a] **3c**
1	Adipic acid	75	87
2	Tartaric acid	60	22
3	Acetonedicarboxylic acid	40	2(48)[b]
4	3-(Carboxymethylthio)propionic acid	240	42
5	2-Ketoglutaric acid	30	8

[a]Isolated yield. [b]*N*-Phenylnortropinone

9-Arylcarbazoles (**4**) were formed by treatment of 1-aryl-

pyrroles (**3**) with **2** in glacial acetic acid. The yield of 4's were summerized depending on the substituent(R) in Table-3.

TABLE-3
PHYSICAL DATA OF 9-ARYLCARBAZOLES **4**

	R	Reflux (h)	Yield (%)[a]	m.p. (ºC)
a	*p*-OCH_3	15	54	149-150
b	*p*-NO_2	28	30	[b]
c	H	19	55	94-96
d	*m*-NO_2	29	24	119-121
e	*m*-Br	18	23	[b]

[a]Isolated yield; [b]Liquid

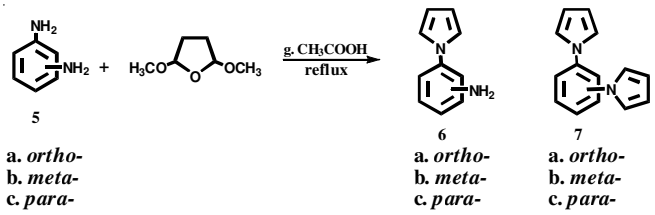
A representative example of synthesis **4** is as the fol-low. The mixture of **3c** (5 mmol) and **2** (10 mmol) was refluxed in glacial acetic acid under N_2 gas for 19 h to afford **4c** in a 55 % yield. Identification of 9-phenylcarbazole by ^{1}H NMR spectrum ($CDCl_3$, Me_4Si) showed **13** proton peaks correspoding to carbazolyl group and phenyl group at δ 7.25-8.18. Mass spectrum showed molecular ion peaks at m/e 243 (100 %).

But the synthesis of 9-alkylcarbazoles from the corresponding 1-alkylpyrroles was not successful. 9-Arylcarbazoles (**4**) scan also be prepared by one-pot reactions of the aromatic amines **1** and **2** in glacial acetic acid under N_2 gas. The results are listed in Table-4. However, the yields from the one-pot reaction are much lower than the reaction from 1-arylpyrroles. In order to synthesize dipyrrolylbenzenes **7a-c** are, reactions of phenylenediamines **5a-c** and 2,5-dimethoxytetrahydrofuran with glacial acetic acid as a catalyst were executed.

TABLE-4
ONE-POT SYNTHESIS OF 9-ARYL CARBAZOLES **4**

	R	Reflux (h)	Yield (%)[a]
a	*p*-OCH_3	12	30
b	*p*-NO_2	20	23
c	H	10	47
d	*m*-NO_2	32	20
e	*m*-Br	18	15

[a]Isolated yield



Scheme-II: Aminophenylpyrroles and dipyrrolylbenzenes

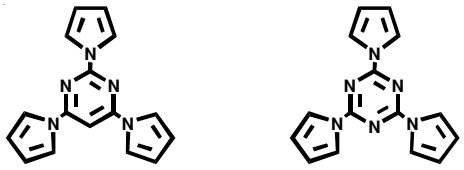
The synthetic results of aminophenylpyrroles **6a-c** and dipyrrolylbenzenes **7a-c** are listed in Table-5.

In case of **5c**, **7c** as a dipyrrolylbenzene was obtained in a 58 % yield but **6c** as a aminophenylpyrrole was not obtained. 2,4,6-Tri-pyrrol-1-yl-pyrimidine (**8**) bearing tripyrrolyl groups was formed by treatment of 2,4,6-triaminopyrimidine and 2,5-dimethoxytetrahydrofuran with glacial acetic acid. Yield of **8** obtained in reflux for 13 h is 37 % and yield of **8** obtained in sealed tube for 0.5 h is 39.5 %. In same synthetic method, 2,4,6-tri-pyrrol-1-yl[1,3,5]triazine (**9**) bearing tripyrrolyl groups was formed in a 29 % yield (in reflux for 13 h) and in a 30 % yield (in sealed tube) (**Scheme-III**).

TABLE-5
PHYSICAL DATA OF AMINOPHENYLPYRROLES **6a-c** AND DIPYRROLYLBENZENES 7**a-c**

Reactant	Solvent	Reflux (h)	Product No.	Yield (%)*	m.p. (ºC)
5a	g.AcOH	6	6a	73	102-103
			7a	5	78-79
5b		1	6b	28	120-122
			7b	37	107-108
5c		1	6c	-	-
			7c	58	213-214

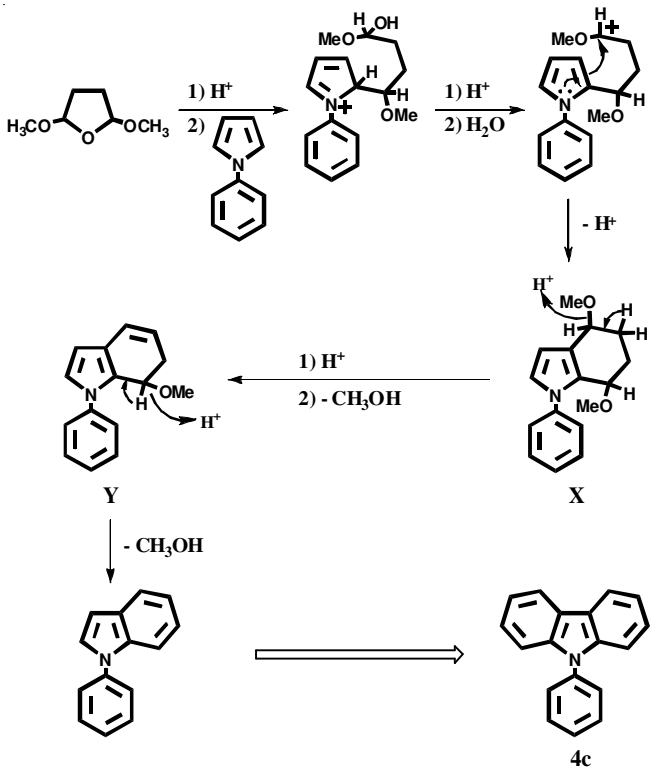
*Isolated yield



8 **9**

Scheme-III: 2,4,6-*Tri*-pyrrol-1-yl-pyrimidine (**8**) and 2,4,6-*tri*-pyrrol-1-yl[1,3,5]triazine (**9**)

In order to investigate the mechanism, the products in the reaction mixture were monitored with time by gas chromatography. 1-Arylindoles were detec-ted by gas chromatography, which were comfirmed with the authentic samples. A possible mechanism for the formation of **4** may involve the cleavage reaction of furan ring by glacial acetic acid and subsequent formation of intermediates X and Y (**Scheme-IV**).



Scheme-IV: Proposed mechanism for the formation of 9-phenylcarbazole **4c**

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