THE REGIOSELECTIVE PHOTOINDUCED AROYLATION AT THE 3-POSITION OF PYRROLE DERIVATIVES[1]

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Abstract ----- Irradiation of arenecarbothioamide with pyrrole or indole derivatives gave regioselectively 3-aroylpyrrole or -indole derivatives, respectively.

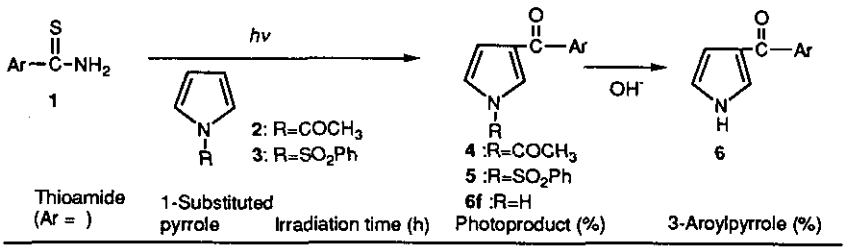
Pyrroles are present in many natural products which exhibit interesting biological activity. Since pyrrole ring system is a "π-excessive" heteroaromatic that electrophiles substitute preferentially at the 1- or 2-position, direct introduction of the substituent at C-3 of pyrrole is difficult.[2] Therefore, new synthetic methods leading to 3-substituted pyrroles have been required.

Recently, Huffman et *al.* have reported the structure-activity relationships of a series of cannabimimetic indoles,[3] and the synthesis of a series of cannabimimetic pyrroles [1-alkyl-3-naphthoyl)pyrroles] by Friedel-Crafts acylation,[4] which are subjected to pharmacological evaluation as non-cannobinoids. The paper[4] on a reinvestigation of the Friedel-Crafts reaction chemistry has prompted us to report some results as an extension of study on the photoinduced aroylation of the five-membered ring systems, as has been already described.[5] Thus the regioselective introduction of a substituent at C-3 of pyrrole and indole ring systems is a subject of considerable interest. We now report the regioselective synthesis of 3-aroyl-pyrroles and -indoles (diaryl ketones) through photoreaction of pyrroles or indoles with various arenecarbothioamides.

In a previous paper,[5b] we reported that irradiation of benzenecarbothioamide (**1a**) with 1-acetylpyrrole (**2**) gave regioselectively 1-acetyl-3-benzoylpyrrole (**4a**) in good yield, and it was found that the lack of photoreactivity of the carbon-carbon double bond in pyrrole ring toward thiocarbonyl was restored by *N*-acetylation of pyrrole. In order to investigate the generality of this aroylation, photoreactions of arenecarbothioamide (**1b-f**) with 1-acetyl- (**2**) or 1-phenylsulfonylpyrrole (**3**) were carried out. The results are listed in Table 1. As expected, the corresponding 3-aroylpyrrole derivatives (**4b-e**, **5a-e**) were obtained in moderate yields (54-89 %), while in the photoreaction of 1-naphthalenecarbothioamide (**1f**) with **2** or **3**, 3-naphthoyl derivative (**6f**) was isolated as 1-deacylated or 1-dephenylsulfonylated form in 55 or 58 %

yields, respectively. The chemical removal of 1-phenylsulfonyl group in **5b-e** was easily and efficiently carried out under mild conditions in the presence of base, affording 3-aroylpyrroles (**6**) almost quantitatively.[6]

Table 1. Photoreaction of Arenecarbothioamide (**1**) with **2**, **3**

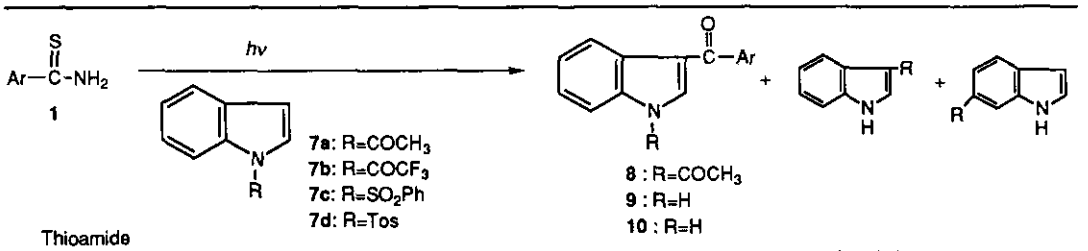


Thioamide (Ar =)	1-Substituted pyrrole	Irradiation time (h)	Photoproduct (%)		3-Aroylpyrrole (%)	
1a	2	20	4a	76		
	3	20	5a	84	6a	98
1b	2	20	4b	56		
	3	20	5b	85	6b	98
1c	2	20	4c	60		
	3	20	5c	89	6c	95
1d	2	20	4d	54		
	3	20	5d	85	6d	96
1e	2	20	4e	61		
	3	20	5e	83	6e	95
1f	2	50	6f	55		
	3	50	6f	58		

Next, as an extension of this reaction, photoreactions of **1a** or **1f** with 1-substituted indole derivatives (**7a-d**) were performed under similar conditions. The results are listed in Table 2. Irradiation of **1a** with 1-acetylindole (**7a**) for 20 h gave 1-acetyl-3-benzoylindole (**8a**) and 3-benzoylindole (**9**) in 35 % and 12 % yields, respectively. In the case of 1-trifluoroacetylindole (**7b**), benzoylated product was also isolated as 1-deacylated form (**9**) in 41 % yield. Further, in the photoreaction of 1-naphthalenecarbothioamide (**1f**) with indole derivatives (**7a,b**) irradiation for 50 h was required, providing 3-naphthoyl derivative (**10**) in 48-53 % yields. On the other hand, in the cases of 1-phenylsulfonylindole (**7c**) and 1-tosylindole (**7d**), 3-benzoylated product was not obtained but photorearranged indole derivatives were isolated in poor yields. To see a photochemical conversion of **8a** to **9**, the **8a** was irradiated under similar conditions for 20 h, but **8a** was recovered unchanged. Similarly, the photochemical conversion of **5a** to **6a** was attempted but failed.

The spectral and physical data of **5a**,[6] **6a**,[2b] **8a**,[8] **9**,[9] and **10**[10] were identical with those reported. The structures of the other photoproducts were also determined on the basis of the spectral and analytical data.

Table 2. Photoreaction of Arenecarbothioamide (**1**) with **7**

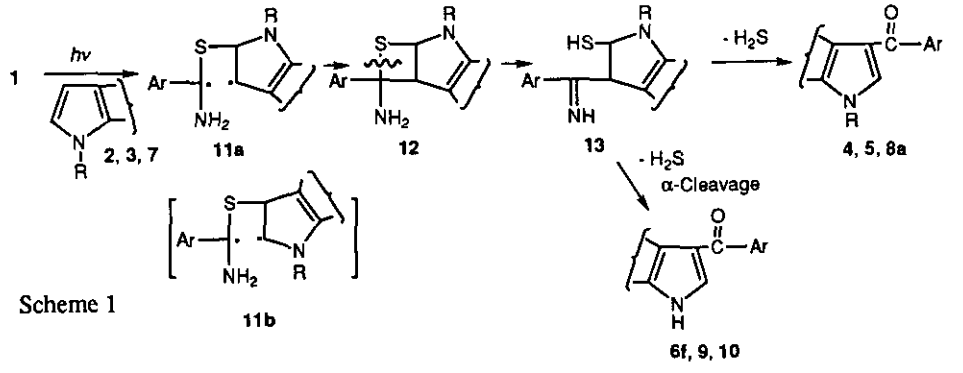


Thioamide (Ar =)	1-Substituted indole	Irradiation time (h)	Photoproduct (%)					
1a	7a	20	8a	35	9	12	18[a]	7[a]
	7b	20			9	41	7[b]	
	7c	20					9[c]	
	7d	20					14[a]	5[a]
1f	7a	50			10	48	23[a]	10[a]
	7b	50			10	53	9[b]	
	7c	50					12[c]	
	7d	50					18[a]	3[a]

a) M. Somei and M. Natsume, *Tetrahedron Lett.*, 1973, 1451.
b) A. Cipiciani, S. Clementi, P. Linda, G. Savelli, and V. Sebastiani, *Tetrahedron*, 1976, 32, 2595.
c) G. Broggini, D. Diliddo, and G. Zecchi, *J. Heterocycl. Chem.*, 1991, 28, 89.

For example, in the ir spectrum of **4d**, absorption bands due to a carbonyl group and an amide moiety appeared at 1670 cm^{-1} and 1645 cm^{-1}, respectively. The ^{13}C-nmr spectrum also supported the presence of the carbonyl group [176.0 ppm(s)] and amide carbonyl group [167.8 ppm(s)], and indicated the presence of pyrrole ring and furan ring.

The formation of 3-aroyl derivatives may be explained as illustrated in Scheme 1. 3-Aroyl derivatives (**4**, **5**, **8a**) arise from the initially formed thietanes (**12**) followed by subsequent photochemical fission of C-S bond of the thietane ring, and then by hydrolysis of generated imines (**13**) during its workup such as chromatography. The thietane formation may be explained in terms of intermediary biradical (**11a**) in parallel to the photoreactions of thioimide systems.[11] The preferential formation of 3-benzoyl derivatives (not 2-benzoyl derivatives) seems to reflect the stability of the generated biradical (**11a**), which should be more stable than **11b**.



Scheme 1

With respect to the formation of 1-deprotected photoproducts (**6f, 9, 10**) two possible pathways might be considered due to the formation of thietane (**12**). In the photolysis of **5a** or **8a**, desulfonylated or deacetylated indole (**9**) was not obtained. This suggested that each of **6f**, **9**, and **10** arose from the imine intermediate (**13**), but not from **5** or **8**.

In the photoreactions of pyrroles (**2** and **3**) with various arenecarbothioamide containing heterocycles, both *N*-acetyl and *N*-phenylsulfonyl groups can serve as good *N*-protecting one though *N*-deacetylation occurred in *N*-acetyl derivatives. In indole derivatives only *N*-acetyl and *N*-trifluoroacetyl groups can serve as useful protecting groups, while *N*-phenylsulfonyl derivative underwent *N*-deprotection reaction in preferential to aroylation of *N*-phenylsulfonylindole to give 3- and 6-phenylsulfonylindoles involving rearrangement.

As described previously, Huffman et *al.* reported that *N*-alkyl-3-(1-naphthoyl)pyrroles synthesized by Friedel-Crafts acylation possess cannabimimetic activity comparable to that of traditional cannabinoides.[4] Thus pyrroles possessing a substituent at the 3-position are biologically interesting compounds, and they can serve as a starting point for the synthesis of more complex derivatives which are otherwise inaccessible by heterocyclic ring construction.

EXPERIMENTAL

All mps were determined on a Yamato mp apparatus (model MP-21) and are uncorrected. Ir spectra were recorded on a JASCO-A-102 spectrophotometer. Nmr spectra were taken on a JEOL JNM EX 400 spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS (0.0 ppm) as an internal standard. The abbreviations used are as follow: s, singlet; d, doublet; q, quartet; m, multiplet. Mass spectra (ms) were obtained on a JEOL JMS-QH-100 gas chromatograph-mass spectrometer. Preparative irradiations were conducted by using a 1 kW high-pressure mercury lamp (Eikosha EHB-W-1000) through a Pyrex filter at room temperature. Stirring of the reaction mixture was effected by the introduction of a stream of nitrogen at the bottom of the outer jacket. Column chromatography was conducted using silica gel (Merck, Kieselgel 60, 70-230 mesh).

Preparation of 1-Substituted Pyrroles and Indoles

Compounds (**2**,[8] **3**,[12] and **7a-d**[13]) were prepared according to the reported procedures.

Irradiation of 1 with 2, 3 or 7: General Procedure

A solution of **1** (5 mmol) and **2** (10 mmol) in benzene (500 ml) was irradiated for 20 h with a 1 kW high-pressure mercury lamp through a Pyrex filter under N_2 at room temperature. After removal of the solvent *in vacuo*, the residue was chromatographed over silica gel (eluent: n-hexane : ethyl acetate = 5 : 1). The results are listed in Tables 3, 5, and 6.

Irradiation of Photoproduct (5, 8a): General Procedure

A benzene (10 ml) solution of **8a** (50 mg) in Pyrex test tube was irradiated for 20 h with a 1 kW high-pressure mercury lamp under N_2 at room temperature. After removal of the solvent *in vacuo*, unchanged **8a** was recovered.

Hydrolysis of Photoproducts (5): General Procedure

A solution of **5a** (330 mg, 1 mmol) in 10 ml dioxane was stirred with 10 ml of 5N NaOH at 25 °C for 24 h. The resulting organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure to give **6a**. The results are listed in Tables 4 and 7.

Table 3. Photoproducts

Photoproduct	Appearance	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
4b	Colorless needles	78.5-80.0	$C_{12}H_{10}N_2O_2$	67.28	4.71	13.08
				(67.39	4.88	13.23)
4c	Colorless needles	67.5-69.0	$C_{12}H_{10}N_2O_2$	67.28	4.71	13.08
				(67.19	4.80	13.01)
4d	Colorless needles	82.0-83.5	$C_{11}H_9NO_3$	65.02	4.46	6.89
				(65.11	4.32	7.01)
4e	Colorless needles	88.5-90.5	$C_{11}H_9NO_2S$	60.27	4.14	6.39
				(60.31	4.00	6.51)
5a	Colorless needles	68.5-70.0 (lit.,[8] 69.0-72.0)				
5b	Colorless plates	97.5-99.0	$C_{16}H_{12}N_2O_3S$	61.54	3.87	8.97
				(61.39	3.92	9.08)
5c	Colorless plates	76.5-78.0	$C_{16}H_{12}N_2O_3S$	61.54	3.87	8.97
				(61.55	3.72	8.88)
5d	Colorless plates	91.5-93.0	$C_{15}H_{11}NO_4S$	59.80	3.68	4.65
				(59.77	3.77	4.80)
5e	Colorless plates	83.5-85.5	$C_{15}H_{11}NO_3S_2$	56.78	3.50	4.42
				(56.59	3.49	4.60)
6f	Colorless plates	79.0-81.0	$C_{15}H_{11}NO$	81.43	5.01	6.33
				(81.29	4.95	6.18)

Table 4 . Aroylpyrroles

Compound	Appearance	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
6a	Colorless plates	99.0-100.0 (lit.,[5b] 99.5-100.0)				
6b	Colorless needles	118.5-120.0	$C_{10}H_8N_2O$	69.75	4.68	16.27
				(69.61	4.53	16.50)
6c	Colorless needles	111.5-113.5	$C_{10}H_8N_2O$	69.75	4.68	16.27
				(69.78	4.79	16.11)
6d	Colorless plates	96.0-97.5	$C_9H_7NO_2$	67.07	4.38	8.69
				(67.11	4.52	8.81)
6e	Colorless needles	92.0-93.5	C_9H_7NOS	61.01	3.98	7.91
				(61.31	4.05	7.95)

Table 5 . Photoproducts

Compound	Appearance	mp (°C)
8a	Colorless plates	103.0-105.0 (lit.,[8] 107.0-108.0)
9	Colorless plates	242.0-244.0 (lit.,[9] 242.0-245.0)
10	Colorless plates	237.0-238.0 (lit.,[10] 236)

Table 6. Spectral Data for Photoproducts

Compound	Ir (cm^{-1})	Ms (M^+) (m/z)	^{1}H-Nmr ($CDCl_3$) δ	^{13}C-Nmr ($CDCl_3$) δ
4c	1680 1640	214	2.60(3H, s), 6.95(1H, m), 7.3-7.5 (2H, m), 7.65(1H, m), 7.90(1H, m) 8.75(1H, m), 9.12(1H, m).	186.2(s), 167.5(s), 152.9(d), 149.2(s), 145.8(d), 128.0(d), 127.8(s), 123.2(d), 121.8(d), 120.2(d), 113.1(d), 22.1(q).
4b	1680 1640	214	2.58(3H, s), 6.90(1H, m), 7.3-7.5 (3H, m), 7.65(1H, m), 8.7-8.9 (2H, m).	187.7(s), 167.7(s), 150.5(dx2), 145.2(s), 127.8(s), 124.8(d), 121.8 (dx2), 120.2(d), 113.4(d), 22.1(q).
4d	1670 1645	203	2.62(3H, s), 6.59(1H, m), 6.95(1H, m), 7.34(2H, m), 7.65 (1H, m), 8.24(1H, m)	176.0(s), 167.8(s), 153.4(s), 146.0 (d), 126.7(s), 124.7(d), 120.0(d), 118.0(d), 113.4(d), 112,4(d), 22.3(q).
4e	1680 1640	219	2.61(3H, s), 6.85(1H, m), 7.18 (1H, m), 7.35(1H, m), 7.67(1H, m), 7.82(1H, m), 7.97(1H, m),	181.3(s), 167.7(s), 144.0(s), 133.2(d), 132.7(d), 128.0(d), 127.8(s), 123.6(d), 120.3(d), 113.5(d), 22.3(q).

Table 6. Continued

5b	1670	312	6.95(1H, m), 7.3-7.6(5H, m), 7.65(3H, m), 7.90(1H, m) 8.75(1H, m), 9.12(1H, m).	186.8(s), 152.0(d), 149.2(s), 145.8(d), 128.4(dx2), 128.2(dx2), 128.0(d), 127.8(s), 125.0(d), 124,5(s), 123.2(d), 121.8(d), 120.8(d), 113.9(d).
5c	1670	312	6.90(1H, m), 7.3-7.5(5H,m), 7.65(1H, m), 7.65(3H, m), 8.7-8.9 (2H, m).	187.7(s), 150.5(dx2), 145.2(s), 128.8(dx2), 128.2(dx2), 127.8(s), 125.0(d), 124.9(s), 124.8(d), 121.8(dx2), 120.2(d), 113.4 (d).
5d	1665	301	6.59(1H, m), 6.95(1H, m), 7.3-7.5(4H, m), 7.6-7.8(4H, m), 8.24(1H, m).	176.0(s), 153.4(s), 146.0(d), 128.4(dx2), 128.2(dx2), 126.7(s), 124.7(d), 124.5(d), 124.1(s), 120.0 (d), 118.0(d), 113.4(d), 112,4(d).
5e	1670	317	6.85(1H, m), 7.1-7.3(3H, m), 7.3-7.5(4H, m), 7.67(1H, m), 7.82(1H, m), 7.97(1H, m).	181.3(s), 144.0(s), 133.2(d), 132.7(d), 128.4(dx2), 128.2(dx2), 128.0(d), 127.8(s), 127.0(d), 126.7 (s), 123.6(d), 120.3(d), 113.5(d).
6f	3400 1680	221	6.5-6.7(3H, m), 7.3-7.5(4H, m), 7.7-7.9(3H, m), 9.50(1H, br s).	173.5(s), 139.1(s), 133.4(s), 130.5 (s), 128.6(d), 128.0(d), 126.2(d), 125.9(d), 125.7(d), 124.8(d), 124.7(d), 124.6(d), 123.1(d), 119.7(d), 106.8(s).

Table 7. Spectral Data for Aroylpyrroles

Compound	Ir (cm^{-1})	Ms (M^+) (m/z)	^{1}H-Nmr (DMSO-d_6) δ	^{13}C-Nmr (DMSO-d_6) δ
6b	1680	172	6.90(1H, m), 7.3-7.5(3H, m), 7.65(1H, m), 8.7-8.9(2H, m), 11.2(1H, br s).	187.7(s), 167.7(s), 150.5(dx2), 145.2(s), 127.8(s), 124.8(d), 121.8 (dx2), 120.2(d), 113.4(d).
6c	1670	172	6.95(1H, m), 7.3-7.5(2H, m), 7.65(1H, m), 7.90(1H, m), 8.75 (1H, m), 9.12(1H, m), 11.8 (1H, br s).	186.2(s), 167.5(s), 152.9(d), 149.2 (s), 145.8(d), 128.0(d), 127.8(s), 123.2(d), 121.8(d), 120.2(d), 113.1(d).
6d	1670	161	6.59(1H, m), 6.95(1H, m), 7.34 (2H, m), 7.65(1H, m), 8.24 (1H, m), 11.5(1H, br s).	176.0(s), 167.8(s), 153.4(s), 146.0 (d), 126.7(s), 124.7(d), 120.0(d), 118.0(d), 113.4(d), 112,4(d).
6e	1687	177	6.85(1H, m), 7.18(1H, m), 7.35 (1H, m), 7.67(1H, m), 7.82(1H, m), 7.97(1H, m), 11.0(1H, br s).	181.3(s), 167.7(s), 144.0(s), 133.2 (d), 132.7(d), 128.0(d), 127.8(s), 123.6(d), 120.3(d), 113.5(d).

ACKNOWLEDGEMENT

This work was supported in part by a Grant-in-Aid for Scientific Research (to M. M.; No. 06672107) from the Ministry of Education, Science and Culture, Japan.

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Received, 9th October, 1995