



SYNTHESIS OF ARYL ACYL-PYRROLE DERIVATIVES-B

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ABSTRACT

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Pyrrole is widely known as a biologically active scaffold which possesses a diverse nature of activities. The combination of different pharmacophores in a pyrrole ring system has led to the formation of more active compounds. Pyrrole containing analogs are considered as a potential source of biologically active compounds that contains a significant set of advantageous properties and can be found in many natural products. The present review highlights the synthetic methods of representatives of nitrogen heterocycles such as pyrrole, substituted pyrroles and other related compounds. The aim of this review is to indicate and summarise the different methods for the synthesis of nitrogen containing heterocycles from the group of pyrrole and pyrrole related structures

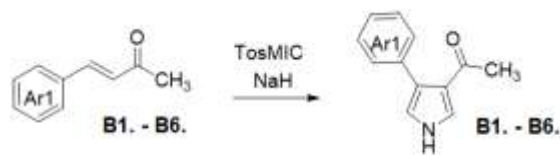
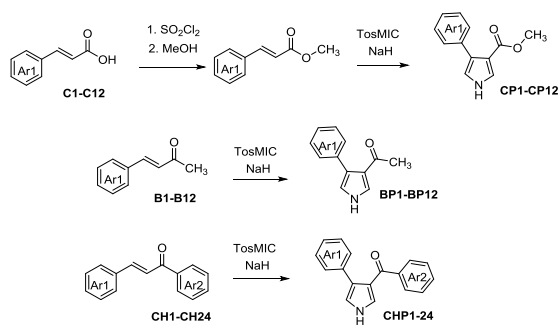
Introduction: Design of synthesis

A significant threat to agricultural production security is caused by insect pests, which not only may result in large financial losses but could also lead to jeopardizing food security for both people and the country as a whole. (1,2) *Spodoptera littoralis* (Boisduval) is an example of dangerous polyphagous moth that may feed on more than 100 host plants from 40 economically important plant families, including cotton, potatoes, maize, vegetables, and ornamental plants, generating production losses of up to 50% due to its larval leaf chewing activities. (3–5) This bug is native to Africa; however, it is distributed worldwide, (6) and its control is becoming more difficult due to resistance, and cross-resistance to chemical insecticides and the bioinsecticide *Bacillus thuringiensis* Berliner. (7,8) Pyrrole derivatives are a noteworthy family of bioactive molecules that have been used in many sectors, including natural product chemistry, pharmaceutical chemistry, and agrochemical chemistry. (9–12) Many natural products containing the pyrrole moiety exhibit a broad range of agrochemical activity, such as ryanodine, pyrrolomycin, and

dioxapyrrolomycin. (13,14) In view of potent biological activities reported for alkaloids of diaryl pyrrole origin, like lamellarins etc. as mentioned in chapter 1, we designed the following synthetic strategy to obtain a library of pyrrole derivatives. Here we used van Leusen reaction on Michael acceptors like cinnamic acids, benzal acetones and chalcones for the preparation of pyrrole derivatives (15). We used cinnamic acids, benzal acetones and chalcones available in our laboratory as starting materials to obtain the target molecules CP1-CP12, BP1-BP12 and CHP1-CHP24. When needed, the starting materials are obtained (bulk up) by following the standard procedures available in the literature. (16-19).

Materials and methods:

All the chemicals were procured from Aldrich Chemical Company (USA), Merck and were used without further purification. The purity of the synthesized was checked by thin layer chromatography (T.L.C.) using mixtures of ethyl acetate and hexane as elutant and visualized in UV-chamber or by using Iodine apor, 2,4D NP orninhydrin.



	code	R1	R2	R3	R4
	BP1.	H	F	F	H
	BP2.	H	OCH ₃	OCH ₃	H
	BP3.	OCH	H	OCH ₃	H
	BP4.	Cl	H	Cl	H
	BP5.	H	OCH ₃	OCH ₃	OCH
	BP6.	3-indolyl			

Scheme: Synthesis of aryl-acetyl 1H-pyrroles from corresponding benzalacetones

The melting points were recorded by using open capillary method on SRS-EZ Meltauto mated melting point instrument and are uncorrected. The IR spectra of the compounds were recorded on BrukerAlphaTFT-IR spectrometer (software-OPUS6.4) using KBr pellet method and the values are expressed in cm^{-1} . The NMR spectra of the compounds were recorded using DMSO- d_6 or CDCl_3 as solvent with tetra methyl silane as internal standard on BRUKERAVANCE400MHz NMR spectrometer (software-Topspin) and chemical shifts were expressed in δ (ppm) Agilent 6410QQQ-ESIMS (software- Mass Hunter) was used for obtaining mass spectra of the compounds.

Synthesis of aryl acyl-pyrrole derivatives (BP1-BP 6):¹

Similar to methyl cinnamates, standard Van Leusen reaction conditions were applied here also to obtain the target pyrrole compounds. The benzal acetone (5 mmol) and TosMIC (5 mmol) are dissolved in 25 mL of diethyl ether: DMSO (2:1). This solution is added dropwise to a stirred suspension of sodium hydride (1.2 equivalents) in 10 mL diethyl ether in ice cold condition. After completion of addition, the temperature is allowed to slowly reach room temperature (~ 15 mins) with continued stirring. Then the reaction was quenched by adding cold water and the mixture is extracted with diethyl ether (10mL X 3). The combined organic extracts are dried over anhydrous MgSO_4 and evaporated to obtain the crude compound. This is further purified by column chromatography to obtain the target compounds. The physicochemical constants and spectroscopy data are provided in **table 1 to 3**.

Table 1: Physicochemical data of the synthesized compounds BP1.-BP6.

C O D E	STRUCTURE	M.F	M.W	M.P	Y %
B P1 .	<p>1-(4-(3,4-difluorophenyl)-1H-pyrrol-3-yl)ethan-1-one</p>	$\text{C}_{12}\text{H}_9\text{F}_2\text{NO}$	221.07	186	9 2
B P2 .	<p>1-(4-(3,4-dimethoxyphenyl)-1H-pyrrol-3-yl)ethan-1-one</p>	$\text{C}_{14}\text{H}_{15}\text{NO}_3$	245.11	181	4 9

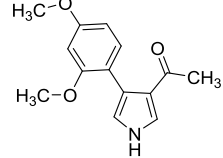
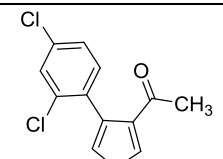
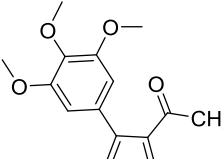
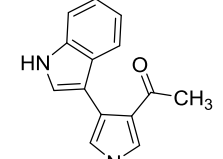
B P3 •	 <p>1-(4-(2,4-dimethoxyphenyl)-1H-pyrrol-3-yl)ethan-1-one</p>	$C_{14}H_{15}NO_3$	245.11	164	4 2
B P4 •	 <p>1-(4-(2,4-dichlorophenyl)-1H-pyrrol-3-yl)ethan-1-one</p>	$C_{12}H_9Cl_2NO$	253.01	172	8 8
B P5 •	 <p>1-(4-(3,4,5-trimethoxyphenyl)-1H-pyrrol-3-yl)ethan-1-one</p>	$C_{15}H_{17}NO_4$	275.12	181	5 1
B P6 •	 <p>1-(4-(1H-indol-3-yl)-1H-pyrrol-3-yl)ethan-1-one</p>	$C_{14}H_{12}N_2O$	224.09	209	3 8

Table 2: IR, Mass and elemental analysis data of the compounds (BP1.-BP6.):

Compound Code	IR(KBr) ν_{max} cm^{-1}	ESIMS m/z positive ion	Elemental analysis		
				Req (%)	Found (%)
BP1.	1176, 1452 (C=C), 1634 (C=O), 2904,	222 (M+1)	C	65.1	65.12
			H	6	4.09
			N	4.10	6.33

	3076 (C-H str), 3205 (N-H str)				
BP2.	1169, 1274 (C-O), 1461 (C=C), 1639 (C=O), 2925, 3062 (C-H str), 3204 (N-H str)	246 (M+1)	C H N	68.5 6 6.16 5.71	68.52 6.14 5.70
BP3.	1174, 1272 (C-O), 1454 (C=C), 1648 (C=O), 2928, 3062 (C-H str), 3210 (N-H str)	246 (M+1)	C H N	68.5 6 6.16 5.71	68.55 6.14 5.70
BP4.	1171, 1452 (C=C), 1636 (C=O), 2902, 3068 (C-H str), 3204 (N-H str)	254 (M+1) 256 (M+3)	C H N	56.7 2 3.57 5.51	56.69 3.54 5.50
BP5.	1176, 1275 (C-O), 1454 (C=C), 1642 (C=O), 2900, 3048 (C-H str), 3212 (N-H str)	276 (M+1)	C H N	65.4 4 6.22 5.09	65.42 6.21 5.06
BP6.	1159, 1455 (C=C), 1635 (C=O), 2928, 3069 (C-H str), 3203 (N-H str)	225 (M+1)	C H N	74.9 8 5.39 12.4 9	74.97 5.36 12.48

Table 3: NMR spectral data of the synthesized compounds BP1-BP12

Compound Code	¹ H-NMR (400MHz, DMSO d ₆)	¹³ C NMR (100MHz, DMSO d ₆)
BP1.	2.53 (s, 3H), 6.98 (s, 1H), 7.19-7.25 (m, 3H), 7.57 (s, 1H), 11.54 (br s, 1H)	28.2, 112.4, 119.2, 120.4, 121.6, 124.4, 127.9, 134.3, 137.8, 143.7, 150.6, 196.9
BP2.	2.47 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 6.99 – 7.09 (m, 2H), 7.18-7.21 (m, 2H), 7.58 (s, 1H), 11.53 (br s, 1H)	28.1, 56.1, 56.7, 110.1, 115.7, 120.5, 120.4, 121.9, 127.6, 129.6, 137.6, 148.7, 149.5, 196.9
BP3.	2.55 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 6.65 (m, 2H), 7.01 (s, 1H), 7.41 (m, 1H), 7.54 (s, 1H), 11.72 (br s, 1H)	28.5, 56.2, 56.6, 101.2, 108.5, 114.9, 118.8, 121.3, 123.9, 131.4, 138.2, 157.4, 159.4, 197.2
BP4.	2.53 (s, 3H), 6.87 (s, 1H), 7.31 (dd J = 2.4, 6.8Hz, 1H), 7.41 (m, 2H), 7.56 (s, 1H), 11.92 (br s, 1H)	28.1, 122.1, 122.5, 128.5, 130.5, 131.7, 132.6, 132.9, 133.3, 136.5, 137.1, 197.7
BP5.	2.52 (s, 3H), 3.82 (s, 9H), 6.89 (s, 2H), 7.01 (s, 1H), 7.54 (s, 1H), 11.58 (br s, 1H)	28.5, 56.8, 60.6, 104.1, 120.6, 121.8, 126.8, 130.2, 137.5, 138.1, 153.6, 197.3
BP6.	2.55 (s, 3H), 6.90 (s, 1H), 7.25-7.29 (m, 2H), 7.39-7.42 (m, 2H), 7.56 (m, 1H), 7.85 (m, 1H), 11.45 (br s, 1H)	28.4, 108.9, 110.8, 112.1, 121.1, 121.8, 122.4, 122.9, 123.6, 124.5, 127.2, 135.2, 137.2, 197.2

3. RESULTS AND DISCUSSION

The van Leusen reaction is a very useful and simple strategy to obtain highly substituted pyrrole derivatives from diverse Michael acceptors possessing polarized double bond. Methyl ester of cinnamic acid, benzalacetone and chalcone were first reported to have successfully formed pyrroles with excellent yield (>80%). The reaction procedure is relatively simple and neat. For cinnamic acids, we prepared the esters by first treating it with thionyl chloride followed by methanol. The product formation is almost 100% and did not need any further purification. The cinnamic esters are then treated with TosMIC in the presence of sodium hydride resulted in the pyrrole. The ¹HNMR spectrum of the pyrrole showed characteristic peaks for the proton at C-2 and C-5 of pyrrole as singlet. In some of the spectra we could observe slight split of the signals as undiscernible triplet. The pyrrole N-H is obtained as a broad singlet above δ8.5ppm. In CDCl₃ it is observed in the range δ8.5-9.5 ppm and in DMSO-d₆ it have gone into much deshielded region at δ10.5-12 ppm. Mass spectral data and elemental analysis completely agree with the structures of the obtained products. CP1, CP4 and CP5 are reported earlier and the remaining is reported for the first time.

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