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Synthesis of Aryl Acyl-Pyrrole Derivatives-B

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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.

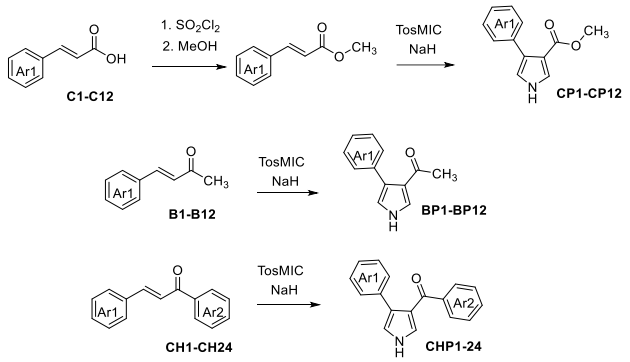
Keywords: Pyrrole, Herterocycles and Bological active compounds synthesis.

1. Introduction

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).



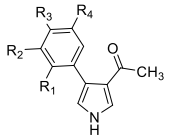
2. Materials and methods:

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 N P orninhydrin. 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 wererecordedonBrukerAlphaTFT-IRspectrometer(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 (BP 1.-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 equivalent) 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

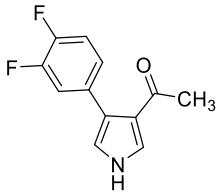
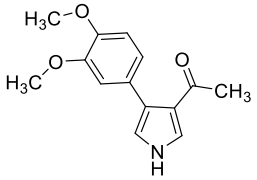
physicochemical constants and spectroscopy data are provided in table 1 to 3.



code	R1	R2	R3	R4
BP1.	H	F	F	H
BP2.	H	OCH_3	OCH_3	H
BP3.	OCH_3	H	OCH_3	H
BP4.	Cl	H	Cl	H
BP5.	H	OCH_3	OCH_3	OCH_3
BP6.	3-indolyl			

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

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

CODE	STRUCTURE	M.F	M.W	M.P	Y %
BP1.	 1-(4-(3,4-difluorophenyl)-1H-pyrrol-3-yl)ethan-1-one	$C_{12}H_9F_2NO$	221.07	186	92
BP2.	 1-(4-(3,4-dimethoxyphenyl)-1H-pyrrol-3-yl)ethan-1-one	$C_{14}H_{15}NO_3$	245.11	181	49

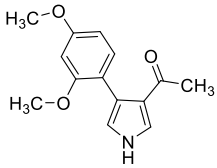
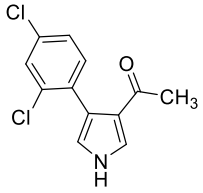
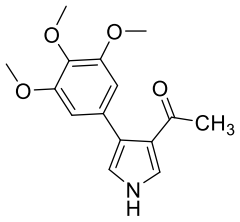
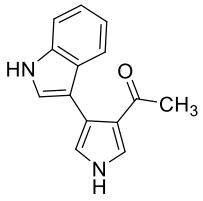
BP3.	 1-(4-(2,4-dimethoxyphenyl)-1H-pyrrol-3-yl)ethan-1-one	$C_{14}H_{15}NO_3$	245.11	164	42
BP4.	 1-(4-(2,4-dichlorophenyl)-1H-pyrrol-3-yl)ethan-1-one	$C_{12}H_9Cl_2NO$	253.01	172	88
BP5.	 1-(4-(3,4,5-trimethoxyphenyl)-1H-pyrrol-3-yl)ethan-1-one	$C_{15}H_{17}NO_4$	275.12	181	51
BP6.	 1-(4-(1H-indol-3-yl)-1H-pyrrol-3-yl)ethan-1-one	$C_{14}H_{12}N_2O$	224.09	209	38

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

Compound Code	IR(KBr) νmax cm−1	ESIMS m/z positive ion	Elemental analysis		
				Req (%)	Found (%)
BP1.	1176, 1452 (C=C), 1634 (C=O), 2904, 3076 (C-H str), 3205 (N-H str)	222 (M+1)	C H N	65.16 4.10 6.33	65.12 4.09 6.33
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	68.56 6.16 5.71	68.52 6.14

			N		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	68.56 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	56.72 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	65.44 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	74.98 5.39 12.49	74.97 5.36 12.48

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

Compound Code	H^1-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 ^{1}HNMR 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 deshieded 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 are reported for the first time.

References

1. Janzen, D. H.; Hallwachs, W. Perspective: Where might be many tropical insects?. Biol. Conserv. 2019, 233, 102– 108
2. Esker, P. Crop loss analysis and global food supply: focusing now on required harvests. CAB Rev. 2012, 7, 44– 52
3. Russell, D. A.; Radwan, S. M.; Irving, N. S.; Jones, K. A.; Downham, M.C.A. Experimental assessment of the impact of defoliation by Spodoptera littoralis on the growth and yield of Giza ’75 cotton. Crop Prot. 1993, 12, 303– 309,
4. EPPO PM 7/124 (1) Spodoptera littoralis, Spodoptera litura, Spodoptera frugiperda, Spodoptera eridania. EPPO Bull. 2015, 45, 410– 444
5. EPPO. EPPO Global Database. Available online: http://gd.eppo.int (accessed on 22 November 2018).
6. Tanani, M.; Hamadah, K.; Ghoneim, K.; Basiouny, A.; Waheeb, H. Toxicity and bioefficacy of Cyromazine on growth and development of the Cotton leafworm Spodoptera littoralis (Lepidoptera: Noctuidae). Int. J. Res. Stud. Zool. 2015, 1, 1– 15
7. Mosallanejad, H.; Smagghe, G. Biochemical mechanisms of methoxyfenozide resistance in the cotton leafworm Spodoptera littoralis. Pest Manage. Sci. 2009, 65, 732– 736
8. Siegwart, M.; Graillot, B.; Lopez, C. B.; Besse, S.; Bardin, M.; Nicot, P. C.; Lopez-Ferber, M. Resistance to bio-insecticides or how to enhance their sustainability: A review. Front. Plant Sci. 2015, 6, 381 DOI: 10.3389/fpls.2015.00381
9. Gholap, S. S. Pyrrole: an emerging scaffold for construction of valuable therapeutic agents. Eur. J. Med. Chem. 2016, 110, 13– 31, DOI: 10.1016/j.ejmech.2015.12.017
10. Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. Pyrrole: a resourceful small molecule in key medicinal heteroaromatics. RSC Adv. 2015, 5, 15233– 15266
11. Ma, Q.; Liu, Y.; Zhang, P.; Li, Y.; Xiong, L.; Wang, Q. Design, synthesis, and biological evaluation of various α-substituted benzylpyrroles based on the structures of insecticidal chlorfenapyr and natural pyrrolomycins. J. Agric. Food Chem. 2014, 62, 6072– 6081
12. Siegwart, M.; Graillot, B.; Lopez, C. B.; Besse, S.; Bardin, M.; Nicot, P. C.; Lopez-Ferber, M. Resistance to bio-insecticides or how to enhance their sustainability: A review. Front. Plant Sci. 2015, 6, 381 DOI: 10.3389/fpls.2015.00381
13. Pepper, B. P.; Carruth, L. A. A new plant insecticide for control of the european corn borer. J. Econ. Entomol. 1945, 38, 59– 66, DOI: 10.1093/jee/38.1.59
14. Charan, R. D.; Schlingmann, G.; Bernan, V. S.; Feng, X.; Carter, G. T. Dioxapyrrolomycin biosynthesis in streptomyces fumanus. J. Nat. Prod. 2006, 69, 29– 33.
15. van Leusen, A. M., Siderius, H., Hoogenboom, B. E. and van Leusen, D. A new and simple synthesis of the pyrrole ring system from Michael acceptors and tosylmethylisocyanides. Tetrahedron Lett.52, 5337-5340 (1972).
16. Gupta, M. and Wakhloo, B.P., Tetrabutylammoniumbromide mediated Knoevenagel

condensation in water: synthesis of cinnamic acids, Arkivoc,94-98 (2007).
17. Pawar, H.S., Wagh, A.S. and Lali, A.M.,Triethylamine: a potential N-base surrogate for pyridine in Knoevenagel condensation of aromatic aldehydes and malonic acid, New J Chem,40(6), 4962-4968 (2016).
18. Handayani, S. and Indyah, S. A., Synthesis of Hydroxyl Radical Scavengers from Benzalacetone and its derivatives, J Phy Sci.19(2), 61–68 (2008).
19. Zhuang C, Zhang W, Sheng C, Zhang W, Xing C, Miao Z. Chalcone: A Privileged Structure in Medicinal Chemistry. Chem Rev.117(12), 7762–7810 (2017).