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A new and efficient one-pot synthesis of indoles

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Abstract

The synthesis of indoles is accomplished in high yields from phenylhydrazines and pyruvic acid using microwave irradiation.

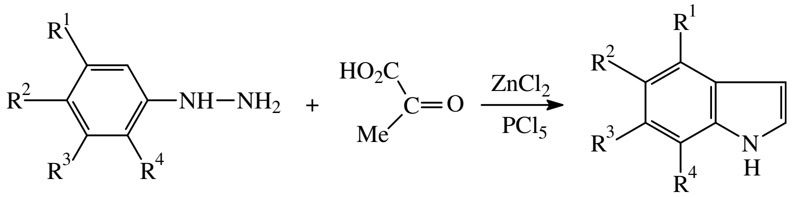
Keywords: Indoles; Phenylhydrazines; Pyruvic acid; Microwaves; Condensation

Indoles and their derivatives are common heterocyclic compounds in nature. The indole ring system is an important structural component in many drugs.[1,2] Indole derivatives are used as neuroprotective agents affecting oxidative stress,[3] potent opioid receptor agonists,[4] highly functionalized pharmacophores,[5] potent PPAR-γ binding agents with potential application for the treatment of osteoporosis,[6] drugs for the treatment of peripheral neuropathy and neurodegenerative diseases,[7,8] glucokinase activators,[9,10] the cytotoxic antibiotic CC-1065 and prodrugs,[11] PPAR-delta activators for the treatment of cardiovascular diseases[12] and dyestuffs.[13,14]

Indoles can be prepared by numerous methods.[15–32] However, all these methods suffer from disadvantages such as long reaction times, difficult to prepare starting materials, use of toxic solvents, significant amounts of waste products, expensive reagents and catalysts.[2]

Previously, we reported organic syntheses in a paste chemical medium and many benefits were apparent.[33] With this in mind, we decided to examine the preparation of indoles by the Fischer method using microwave irradiation. As starting materials, we used pyruvic acid, phenylhydrazines and phosphorus pentachloride. These reagents are polar and absorb microwaves readily to form indoles, Scheme 1.

Condensation of pyruvic acid with phenylhydrazines gives pyruvic acid phenylhydrazones.[34,35] Zinc chloride is a Lewis acid catalyst and accelerates the formation of the new carbon–carbon bond in the phenylhydrazone intermediates, which are transformed in indole-2-carboxylic acids.[36] Phosphorus pentachloride functions as a water



Scheme 1.

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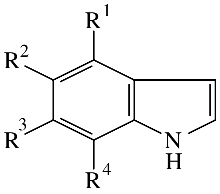
scavenger and, the resulting by-product, phosphoric acid, also catalyses the indole synthesis.[37,38]

Usually, the decarboxylation of indole-2-carboxylic acid takes place at very high temperature by pyrolysis or

Table 1
Synthesis of indoles



Entry	R^1	R^2	R^3	R^4	Elemental analysis calculated/found			Time (min)	Yield (%)	IR (cm^{-1})	^1H NMR δ(ppm); J (Hz)	Mp (°C)
					%C	%H	%N					
1	H	H	H	H	82.05 82.04	5.98 5.96	11.96 11.95	4	88			51–53[48] 51
2	H	H	H	Me	82.44 82.41	6.87 6.85	10.68 10.67	4	71	3401vs (NH) 2991w 1450m 782vs	2.34 (s, 3H, CH_3) 6.54 (d, $J = 8$, 1H, H-3) 7.10 (d, $J = 8$, 1H, H-2) 6.79 (dd, 1H, $J = 7.7$, $J = 1.4$, H-6) 6.85 (dd, 1H, $J = 7.9$, $J = 7.7$, H-5) 7.34 (dd, 1H, $J = 7.9$, $J = 1.4$, H-4) 8.12 (br s, 1H)	80–82[20] 81
3	H	NO_2	H	H	59.25 59.22	3.70 3.69	17.28 17.26	5	79	3307vs (NH) 2998w 1550s (NO_2^{as}) 1498m 1323vs (NO_2^{s}) 743s	6.61 (d, $J = 8.3$, 1H, H-3) 7.20 (d, $J = 8.3$, 1H, H-2) 7.69 (d, $J = 8.3$, 1H, H-7) 7.99 (dd, $J = 8.3$, $J = 1.5$, 1H, H-6) 8.41 (d, $J = 1.5$, 1H, H-4) 8.83 (br s, 1H, NH)	134
4	H	H	H	NO_2	59.25 59.21	3.70 3.67	17.28 17.27	5	71	3400vs (NH) 3003w 1517s (NO_2^{as}) 1475 1320vs (NO_2^{s}) 707s	6.57 (d, $J = 8.2$, 1H, H-3) 7.16 (dd, $J = 8.2$, $J = 8.1$, 1H, H-5) 7.18 (d, $J = 8.2$, 1H, H-2) 7.88 (dd, $J = 8.2$, $J = 1.7$, 1H, H-4) 8.01 (dd, $J = 8$, $J = 1.7$, 1H, H-6) 9.03 (br s, 1H)	101
5	H	H	H	Cl	63.36 63.33	3.96 3.92	9.24 9.22	5	80	3396vs (NH) 2873w 1429s 751vs	6.51 (d, $J = 7.5$, 1H, H-3) 7.11 (dd, $J = 7.5$, $J = 1.4$, 1H, H-6) 6.95 (dd, $J = 7.9$, $J = 7.5$, 1H, H-5) 7.14 (d, $J = 7.5$, 1H, H-2) 7.41 (dd, $J = 7.9$, $J = 1.4$,1H, H-4) 8.23 (br s, 1H)	58
6	H	Br	H	H	48.97 48.95	3.06 3.05	7.14 7.12	4	83	3407vs (NH) 2970w 1450s 767vs	6.52 (d, $J = 7.4$, 1H, H-3) 7.11 (d, $J = 7.4$, 1H, H-2) 7.21 (dd, $J = 8$, $J = 1.2$, 1H, H-6) 7.27 (d, $J = 8$, 1H, H-7) 7.69 (d, $J = 1.2$, 1H, H-4) 9.12 (br s, 1H)	91
7	H	F	H	H	71.11 71.09	4.44 4.43	10.37 10.34	5	84	3401vs (NH) 2985w 1442s 773vs	6.54 (d, $J = 7.6$, 1H, H-3) 7.15 (d, $J = 7.6$, 1H, H-2) 6.71 (dd, $J = 8.3$, $J = 1.5$, 1H, H-6) 7.22 (d, $J = 1.5$, 1H, H-4) 7.30 (d, $J = 8.3$, 1H, H-7) 8.94 (br s, 1H)	45
8	MeO	H	MeO	H	67.79 67.77	6.21 6.17	7.90 7.89	5	79	3410vs (NH) 3925w 1464s 1017vs (C–O–C^{s}) 1246vs (C–O–C^{as}) 780vs	3.69 (s, 3H, 4-OCH_3) 3.72 (s, 3H, 6-OCH_3) 6.51 (d, $J = 7.8$, 1H, H-3) 7.03 (d, $J = 7.8$, 1H, H-2) 6.01 (d, $J = 1.6$, 1H, H-5) 6.42 (d, $J = 1.6$, 1H, H-7) 8.87 (br s, 1H)	119

thermolysis reactions,[39–42] iodinative decomposition[43] or, under mild conditions, by enzyme reactions.[44,45] In our method, the decarboxylation takes place in a paste chemical medium during the microwave irradiation.

Initially, pyruvic acid, phenylhydrazine derivative, and zinc chloride were mixed thoroughly. Next, phosphorus pentachloride was added and the mixture stirred further. A paste like material resulted which was irradiated with microwaves.[46] The hot spots created in a paste during the microwave irradiation act like catalytic centers[33,47] resulting in the formation of the corresponding indoles in high yields.

The combination of simple experimental, easy separation of the indoles, high product purity, short reaction time, and high yields are advantages of this method. The synthesized products are shown in Table 1.

Synthesis of indoles, a general procedure: Phenylhydrazine (3 mmol), pyruvic acid (3.5 mmol), and zinc chloride (0.6 mmol) were thoroughly mixed in a 25 ml Pyrex beaker. Next, phosphorus pentachloride (1 mmol) was added and mixing was continued until a paste resulted. The paste was irradiated in a microwave oven ($\lambda = 12.2$ cm) for the required time (see Table 1). Water (50 ml) was added and the aqueous extracted with dichloromethane (50 ml × 2). The combined extracts were dried (sodium sulfate) and the solvent evaporated. The residue was recrystallized from ether to give the indole derivatives (Table 1).

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