
A One Pot Synthesis of Arylindoles by Bischler Indoles Synthesis Under Coupled Microwave Phase Transfer Catalysis

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Abstract

In this communication, a simple 'One Pot' synthesis of arylindoles (3a - i) by Bischler Indole synthesis via microwave Phase Transfer Catalysis is being reported. A mixture of *n* - TBAHSO₄, KOH in catalytic amount, aniline, *o* - bromoacetophenones were irradiated with microwaves for 5 -6 minutes at full power (800 W). PTC coupled with microwaves showed enhanced yields, the clean reaction conditions require less time & have easier workup protocol. All synthesized compounds were characterized by their Proton Magnetic Resonance (PMR), IR, FAB Mass and elemental analyses.

Keywords - Arylindoles, Microwave, Bischler Indole Synthesis, Solid - Solid Phase Transfer Catalysis.

Introduction

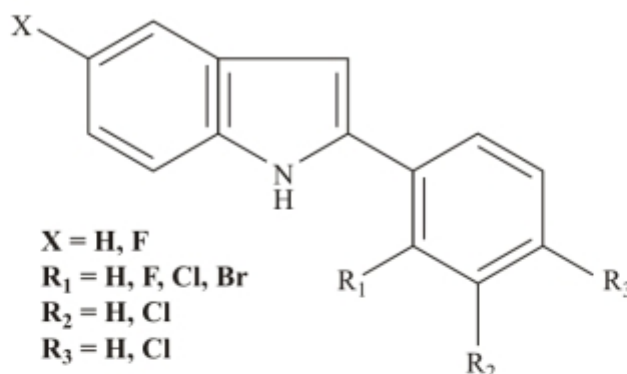
The indoles especially the halogenated indole derivatives are a very active area of research in view of their widespread occurrence in nature. Indole derivatives display a wide spectrum of biological activities viz., antibacterial (Tanaka *et al.*, 2006), antiviral (Giampieri *et al.*, 2009; Boriskin *et al.*, 2008), anti-inflammatory (Guerra *et al.*, 2011; Rani *et al.*, 2004), antidiabetic (Henke *et al.*, 1999), antifertility (Joshi *et al.*, 1986), anticancer (Shoeb *et al.*, 2006), antidepressant (Dunsdon *et al.*, 1985). Various 3-indolylglyoxamides possess CNS depressant (Archibald *et al.*, 1974) and many other pharmacological activities (Damerson *et al.*, 1976). Tryptamine (3- β -aminoethylindole) is known to exhibit antiserotonin (Grinev *et al.*, 1967), adrenolytic (Wolley *et al.*, 1953) and anticancer activity (Wan-Ru *et al.*, 2007; Gunasekera *et al.*, 1980). Indole derivatives are found in most of the naturally occurring alkaloids such as reserpine, LSD, psilocin, psilocybin, harmine, etc.

The need for new, more economic synthetic methods for the preparation of important pharmaceuticals and agrochemicals in chemical industry is universally acknowledged and much progress has already been made in this field. Besides, the traditional procedures (Wagaw *et al.*, 1998), modern emphasis is on methods that rely on the transition metal-catalyzed cyclization of *o*-alkynylanilines, although these procedures have the disadvantage of requiring one or several steps involving the use of stoichiometric amounts of metals to introduce the *ortho* side chain prior to the cyclization, and also that they normally require a nitrogen protecting group. Some copper (Dai *et al.*, 2003) or palladium (Hong *et al.*, 2004) catalyzed domino protocols are known for the transformation of N-protected 2-iodoanilines into indoles, without the need to isolate *o*-alkynyl intermediates. However, the preparation of the starting materials from commercially available anilines is still necessary.

Previously indoles were synthesized by Fischer indole (Li *et al.*, 2009) synthesis which requires aryl methyl ketones and substituted phenylhydrazines to introduce various substituents in the indolyl moiety. Since, these aryl hydrazines are very unstable and their preparation is quite tedious leading to lower yields. We herein report the synthesis of various substituted 2-arylindoles especially 5-fluoro-2-arylindoles by Bischler indole synthesis (Sridharan *et al.*, 2006) coupling Phase Transfer Catalysis with microwave irradiation. PTC allows one to perform many reactions that otherwise proceed unsatisfactorily or do not proceed at all due to the reactants being present in different phases. It minimizes the two important deactivating forces viz. solvation & ion - pairing. PTC is now well established as a 'Green Chemistry Technique'. PTC coupled with non - conventional energy like microwaves offers the advantage of accomplishing reaction at ambient pressure, thus providing unique chemical process with special attributes such as enhanced reaction rates, higher yields and the associated ease of manipulation.

This work is in continuation to our earlier work on bioactive heterocycles and phase transfer catalysis (Pathak *et al.*, 2007; Pathak *et al.*, 2009). We thought it worthwhile to synthesize potentially bioactive indole derivatives containing fluorine *via* microwave assisted solventless solid-solid PTC. Since the compounds may be potentially bioactive they would be sent for screening for their anti - inflammatory & anti - tumor activities. PTC, microwave all are now recognized as environmentally benign alternatives to conventional methods. In conclusion, we describe a general, economical and environmentally friendly protocol for the one pot preparation of 2-arylindoles from anilines under mild conditions, using solvent - free reaction conditions affording higher yields in comparison with the traditional conditions. Moreover, the elusive 5/6-substituted derivatives can easily be prepared which can be further utilized to synthesize pharmaceutically important 5/6-substituted tryptamine derivatives.

This paper deals with the synthesis and spectral studies of various substituted ω -bromoacetophenones (2a-f) and 5-substituted-2-arylindoles (3a-i). The following types of compounds have been synthesized.

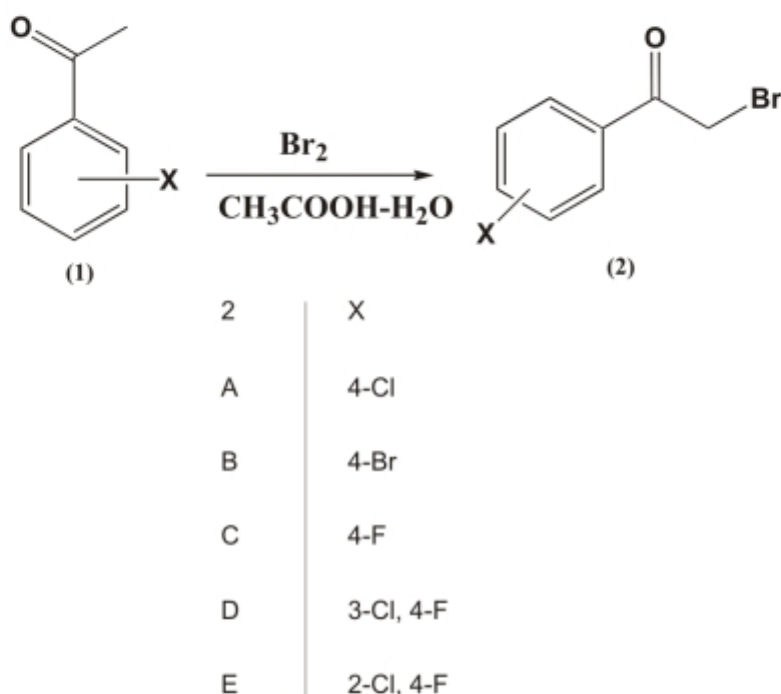


All the synthesized compounds have been characterized on the basis of their IR, 1H NMR, FAB Mass spectral data and elemental analyses.

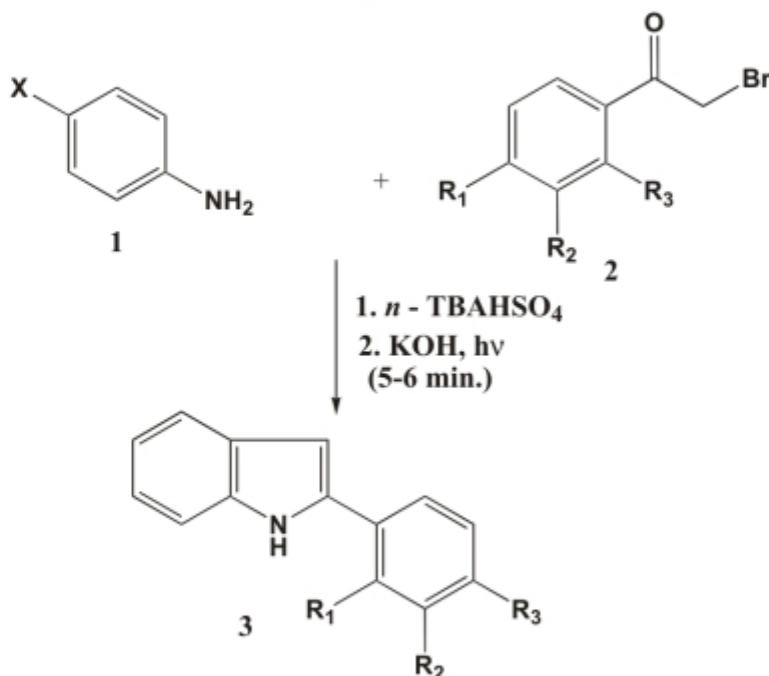
Result and Discussion

A survey of literature revealed that no work has been done on the synthesis of fluorine containing 2-arylindoles via microwave assisted solid-solid phase transfer catalysis. Therefore, an attempt to synthesize fluorinated 2-arylindoles by microwave assisted solid-solid phase-transfer catalysis was made in which the reactions are completed within only a few minutes and afford the products in high yields. A series of substituted ω -bromoacetophenones (2a-e) and 5-substituted-2-arylindoles (3a-i) have been prepared and characterized. The appropriately substituted ω -bromoacetophenones were prepared by treatment of substituted acetophenones with bromine in glacial acetic acid-water at 25-30°C

(Scheme-I). 5-Substituted - 2-arylindoles (3a-i) have been prepared by microwave solventless solid-solid PTC approach. They are prepared by Bischler Indole Synthesis. They are formed when 2:1 mixture of the suitable aniline (1) and substituted ω -bromoacetophenones (2) are irradiated for 5-6 minutes at full power (800 W) in the presence of PTC condition (KOH and *n*-TBAHSO₄) in improved yields and lesser time. All the synthesized compounds gave single spot on TLC in different solvent systems. The synthetic steps are illustrated in the following Schemes – I and II respectively.



Scheme – I



3	X	R1	R2	R3
A	H	H	H	H
B	H	Cl	H	H
C	H	Br	H	H
D	H	F	H	H
E	H	F	Cl	H
F	H	F	H	Cl
G	F	H	H	H
H	F	Br	H	H
I	F	Cl	H	H

Scheme II

The names and m. p.'s of all synthesized compounds are recorded in Table 1.

Table 1: Physical characteristics of 5 – substituted – 2 – arylindoles (3a – i)

Compd. No.	Name	Molecular formula	M. P. (°C)	Yield (%)	Ref. No.	C% Calcd./ found	H% Calcd./ found	N% Calcd./ found
3a	2 – Phenylindole	C ₁₄ H ₁₁ N	182	79	47, 48, 49	87.05/ 87.01	5.70/ 5.68	7.25/ 7.22
3b	2 – (4-Chlorophenyl)indole	C ₁₄ H ₁₀ ClN	208	83	50	73.68/ 73.72	4.39/ 4.40	6.14/ 6.17
3c	2 – (4-Bromophenyl)indole	C ₁₄ H ₁₀ BrN	199	88	47	61.76/ 61.78	3.68/ 3.67	5.15/ 5.16
3d	2 – (4-Fluorophenyl)indole	C ₁₄ H ₁₀ FN	188	86	51	79.62/ 79.58	4.74/ 4.75	6.64/ 6.62
3e	2 – (3 – Cloro - 4- fluorophenyl) indole	C ₁₄ H ₉ ClFN	179	65	52	68.43/ 68.47	3.67/ 3.68	5.70/ 5.71
3f	2 – (2-Chloro – 4 - fluorophenyl) indole	C ₁₄ H ₉ ClFN	193	67	52	68.43/ 68.40	3.67/ 3.66	5.70/ 5.68

3g	5 – Fluoro – 2-phenylindole	C ₁₄ H ₁₀ FN	212	57	-	79.62/ 79.65	4.74/ 4.75	6.64/ 6.65
3h	5 – Fluoro – (4 – chlorophenyl) indole	C ₁₄ H ₉ ClFN	225	55	-	68.43/ 68.41	3.67/ 3.68	5.70/ 5.72
3i	5 – Fluoro – (4 – bromophenyl) indole	C ₁₄ H ₉ BrFN	218	59	-	57.93/ 57.91	3.10/ 3.08	4.33/ 4.31

The IR spectra of substituted ω -bromoacetophenones (2a-e) showed absorption band in the region of 1700 – 1690 cm⁻¹ which is attributed to >C=O stretching vibrations. Aromatic C-H stretching absorption peak appears in the region of 3050 – 3025 cm⁻¹. The appearance of two new bands at 2830 cm⁻¹ and 540 cm⁻¹ corresponding to aliphatic and C-Br stretching, respectively, confirms the formation of substituted ω -bromoacetophenones. Aromatic >C=C< absorption band is observed in the region of 1610 – 1590 cm⁻¹. In the IR spectra of 5- substituted – 2 – arylindoles (3a-i) two new strong bands are observed, one band is due to -NH stretching between 3450 – 3410 cm⁻¹ and another between 1200 – 955 cm⁻¹ region have been assigned to C-N frequencies. The strong band in the region between 1275 – 1200 cm⁻¹ has been attributed to Ar-F stretching modes. All other absorption bands remain unaltered.

In ¹H NMR spectra of substituted ω -bromoacetophenone (2a-e) resonance signal due to -COCH₃ disappeared from δ 2.61 ppm and -CH₂ resonance signal appeared from δ 4.0 – 4.5 ppm. In the ¹H NMR spectra of 5- substituted – 2 – arylindoles (3a-i), a broad singlet due to N-H proton is observed in the region of δ 7.8 – 8.2 ppm (confirmed by D₂O exchange). Disappearance of -CH₂ proton and appearance of methine proton at C-3 position of indole moiety from δ 6.35 – 6.8 ppm supports the formation of desired compounds (3a-i). Aromatic protons are observed as multiplet from δ 6.8 – 7.7 ppm. Additional support was obtained by mass spectral data where the expected molecular ion peaks corresponding to appropriate molecular weight of derivative confirmed the formation of the compounds.

The IR, ¹H NMR and FAB mass spectral data of 5- substituted – 2 – arylindoles are given in Table 2.

Table 2: Spectral data of 5 – substituted – 2 – arylindoles (3a – i)

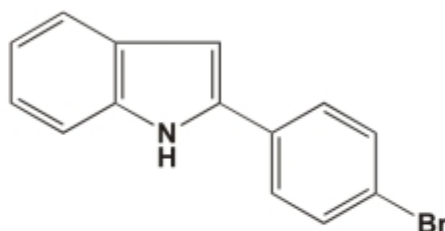
Compd. No.	IR (KBr) ν_{\max} cm ⁻¹	¹ H NMR (CDCl ₃) δ ppm	FAB Mass m/z (M++1)
3a	3410 (br, NH), 3025 (Ar-H str.), 1590 (C=C str.), 1000 (C-N str.)	6.35 (s, CH, 1H), 7.7 (s, NH, 1H), 6.8-7.2 (m, Ar-H, 9H)	194
3b	3425 (br, NH), 3027 (Ar-H str.), 1606 (C=C str.), 1175 (C-N str.), 790 (C-Cl str.)	6.6 (s, CH, 1H), 8.2 (s, NH, 1H), 6.9-7.5 (m, Ar-H, 8H)	229 / 231*
3c	3420 (br, NH), 3031 (Ar-H str.), 1605 (C=C str.), 1010 (C-N str.), 575 (C-Br str.)	6.4 (s, CH, 1H), 7.9 (s, NH, 1H), 6.9-7.4 (m, Ar-H, 8H)	273 / 275*
3d	3430 (br, NH), 3035 (Ar-H str.), 1610 (C=C str.), 1200 (C-N str.), 1,200 (C-F str.)	6.65 (s, CH, 1H), 8.1 (s, NH, 1H), 6.9-7.5 (m, Ar-H, 8H)	212

3e	3415 (br, NH), 3040 (Ar-H str.), 1610 (C=C str.), 1195 (C-N str.), 1,275 (C-F str.), 800 (C-Cl)	6.7 (s, CH, 1H), 8.3 (s, NH, 1H), 6.9-7.7 (m, Ar-H, 7H)	246 / 248*
3f	3420 (br, NH), 3042 (Ar-H str.), 1608 (C=C str.), 1193 (C-N str.), 1,276 (C-F str.), 801 (C-Cl)	6.75 (s, CH, 1H), 8.4 (s, NH, 1H), 6.8-7.8 (m, Ar-H, 7H)	246 / 248*
3g	3430 (br, NH), 3038 (Ar-H str.), 1601 (C=C str.), 1185 (C-N str.)	6.75 (s, CH, 1H), 8.4 (s, NH, 1H), 6.8-7.8 (m, Ar-H, 8H)	212
3h	3445 (br, NH), 3050 (Ar-H str.), 1607 (C=C str.), 1195 (C-N str.), 1,240 (C-F str.), 790 (C-Cl)	6.8 (s, CH, 1H), 7.6 (s, NH, 1H), 7.5-7.9 (m, Ar-H, 7H)	246 / 248*
3i	3440 (br, NH), 3042 (Ar-H str.), 1607 (C=C str.), 1190 (C-N str.), 1,250 (C-F str.), 580 (C-Br)	6.8(s, CH, 1H), 7.5 (s, NH, 1H), 7.3-7.9 (m, Ar-H, 7H)	291 / 293*

Experimental

Melting points were recorded in open glass capillaries and are uncorrected. IR spectra ($4000\text{--}400\text{ cm}^{-1}$) were recorded on a Perkin-Elmer Model – 557 and Nicolet – Magna Model – 750 spectrophotometer in KBr pellets at Central Drug Research Institute (CDRI), Lucknow and Department of Chemistry, University of Rajasthan, Jaipur. ^1H NMR spectra were recorded on Bruker DRX 300 NMR spectrophotometer (300 MHz FT NMR) at CDRI, Lucknow and on Jeol FX 90 Q spectrophotometer at Department of Chemistry, University of Rajasthan, Jaipur using CDCl_3 / DMSO as solvent. TMS was taken as internal standard. The chemical shifts are in δ ppm. FAB mass spectra were recorded on Jeol SX-102 (FAB) mass spectrometer at CDRI, Lucknow using *m*-nitrobenzyl alcohol as matrix. All compounds are homogenous on thin - layer chromatography (TLC) in various solvent systems.

Synthesis of 2 – (4 - Bromophenyl) indole (3c)



It was prepared by Bischler Indole Synthesis. A mixture of *n*-TBAHSO₄ and KOH in catalytic amount (5 mol%) were grinded together in a mortar. Then this mixture was transferred into a conical flask (100 mL). Aniline (20 mmol, 1.86 g) and 4 – Bromo – ω – bromoacetophenone (10 mmol, 2.62 g) was added into it and irradiated with microwaves for 5-6 minutes at full power (800 W). Final temperature of the reaction was measured with the help of thermometer at the end of reaction. The progress of reaction was monitored by TLC using C_6H_6 : pet - ether :: 90 : 10 as solvent system. After cooling to room temperature the reaction mixture was extracted using chloroform and the product was purified from column chromatography using pet - ether (B.P. $60\text{--}80^\circ\text{C}$) as eluent.

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