



Application of Microwave Synthesizer in the Synthesis of 4-Hydroxy Indole a Pharmaceutically Important Intermediate of Pindolol

Jasmin K Khatri^{1*}, Suhas R Pednekar² and Ramesh S Chaughule¹

¹Organic Chemistry Research Laboratory, Ramnarain Ruia Autonomous College, Mumbai, India

²Vice-chancellor, University of Mumbai, Kalina Campus, Mumbai, India

*Corresponding Author: Jasmin K Khatri, Organic Chemistry Research Laboratory, Ramnarain Ruia Autonomous College, Mumbai, India.

DOI: 10.31080/ASMS.2022.06.1365

Received: August 05, 2022

Published: August 30, 2022

© All rights are reserved by Jasmin K Khatri, et al.

Abstract

Indole heterocycles are found to show varied biological application including anti-cancer, antibacterial, anti-viral etc. properties. Synthesis of Pindolol is a simple two step process from the key intermediate 4-Hydroxy Indole which takes place in aqueous media under mild condition. However, synthesis of 4-Hydroxy Indole emerged out to be our area of interest. Microwave assisted dehydrogenative aromatization of an oxoindole to hydroxyindole in a two step reaction using copper (II) bromide and then Lithium bromide with lithium carbonate has been carried out with reasonable good yields within minutes of focused microwave irradiation, thereby, revealing the benefit of saving energy and time.

Keywords: Microwave Synthesizer; Dehydrogenative Aromatization; Hydroxy Indole; Copper (II) Bromide; Bromination; Active Substance Related Substances; Pharmacological

Abbreviations

m.p.: Melting Point; Ar: Aromatic; br: Broad; ppm: Parts Per Million; mmol: Milli Mol

Introduction

Due to the fact that heterocyclic ring structures are frequently found in biologically active compounds, they have garnered a lot of attention. A quick review of the most potent pharmacophores reveals that the most common type of physiologically significant small compounds are heterocycles based on nitrogen [1]. N-heterocycles continue to serve as scaffolding for chemicals with intriguing biological properties and are employed in a variety of therapeutic contexts [2]. These ring systems have numerous uses, including anti-fungal, anti-bacterial, and anti-cancer agents as well as vitamins and herbicides. It has been a constant goal to create more effective synthetic processes [3]. Finding effective

and gentle ways for the manufacture of heterocycles is becoming increasingly crucial for scientists working on the development of organic molecules.

The indole heterocycle exhibits anti-cancer, anti-bacterial, anti-viral, anti-inflammatory, and anti-migraine properties in biological applications [4]. Pharmaceuticals, herbicides, electronic materials, and polymeric materials are just a few of the many applications for phenols, a significant class of aromatic compounds. Although there are numerous traditional and contemporary techniques for creating and altering the structure of the phenol scaffold, the simple preparation of phenols with a variety of structural characteristics continues to spark interest.

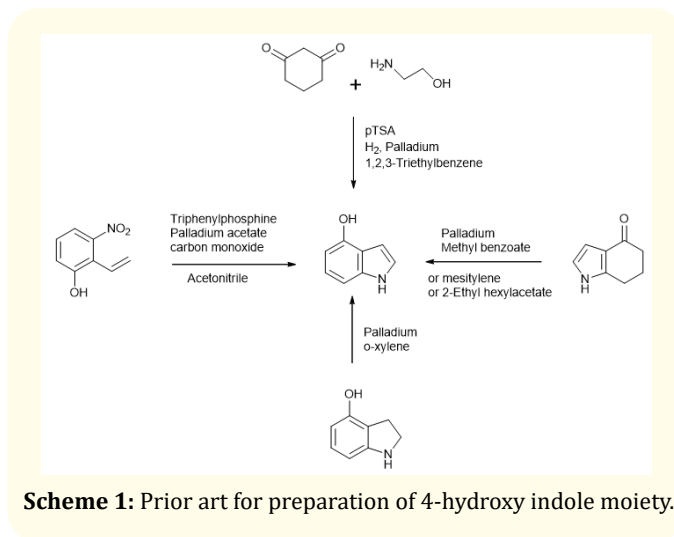
One of the most significant oxidative transformations in organic synthesis is dehydrogenative aromatization, and since cyclohexanones are both affordable and stable, they are frequently

used as raw materials to create a variety of significant bulk chemicals, such as aromatic phenols and their derivatives [5-9]. The ability of cyclohexanones to be dehydrogenated into phenol has long been understood. In fact, the conversion of cyclohexanones to phenols first occurred in the early 20th century [10-12], with chloranil and DDQ serving as the standard and practical reagents for stoichiometric dehydrogenation [13,14]. To prepare, α,β -unsaturated ketones, which go through a second dehydrogenation, followed by tautomerization to yield the desired phenol product, requires stoichiometric and laborious substitution reactions of the α -position of ketones with halogens, sulphur, and selenium groups, with the subsequent elimination of these groups [15]. However, the majority of reported techniques for producing phenols by oxidatively dehydrating cyclohexanones have only had moderate success in terms of atom economy. Particularly for synthesis on a large scale in chemical industry, the low yields, use of a stoichiometric reagent as a hydrogen acceptor, harsh reaction conditions, and prolonged reaction time are undesirable.

A number of reactions have been reported where hydroxy indoles have been synthesized from their corresponding ketones i.e. aromatization from respective cyclohexanones using different reaction conditions. In few of the recent publications Hundsdorfer, Claas., *et al.* [16] used DDQ in Dioxane, while Zacuto, Micheal J. and Cai, Dongwei [17] used Iodine in methanol, whereas Eric D.Edstrom., *et al.* [18] use DDQ in Benzene-Dichloromethane for aromatization to take place.

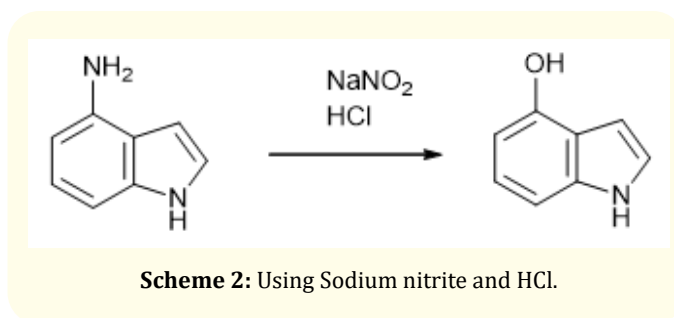
Now realizing of the pharmaceutical importance of the Indole moiety during literature search, it was realised that 4-Hydroxy Indole is a very important intermediate in the manufacturing of an active pharmaceutical substance 'Pindolol' i.e. 1-(1H-indol-4-yloxy)-3-(propan-2-ylamino)propan-2-ol. Synthesis of Pindolol is a simple two step process from the key intermediate 4-Hydroxy Indole which takes place in aqueous media under mild condition. However, Synthesis of 4-Hydroxy Indole emerged out to be our area of interest. An extensive literature search shows that there were many strategies available to build up this moiety by Catalytic hydrogenation using palladium [19-23] (Scheme 1).

Other strategies by Somei Masanori., *et al.* [24] involve use of sodium nitrite and hydrochloric acid (Scheme 2). This combination is more likely to generate Nitrosamine impurity in



Scheme 1: Prior art for preparation of 4-hydroxy indole moiety.

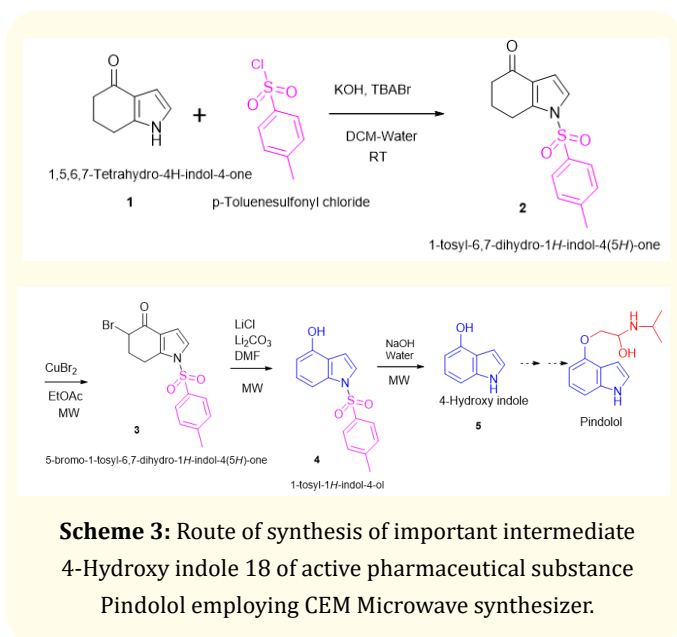
contact with secondary amine (-NH group of Indole). We know that Nitrosamines are a major coherent of concern for the entire Medical/Pharmaceutical industry.



Scheme 2: Using Sodium nitrite and HCl.

In the quest to search for route of synthesis which is different from the route mentioned above and can be tried on microwave synthesizer, we have selected the following reaction which involves dehydrogenative aromatization of an oxindole to hydroxyindole in a two step reaction using copper(II) bromide and then Lithium bromide with lithium carbonate have been employed for aromatization reaction (Scheme 3). Matsumoto., *et al.* has reported this conversion with excellent yield. We wanted to evaluate the impact of Microwave on the rate of reaction. This type of conversions has not been reported on microwave synthesizer.

Furthermore, shorter reaction times allow optimization studies since we can quickly analyze the influence of various factors in the reaction condition on the yield of the desired product produced, saving valuable time and energy.



Materials and Methods

Microwave radiation has been used effectively in the past for the enhancement of reactivity and in certain cases has resulted in the formation of a product that under normal conditions would not be possible. Rapid advancements taking place in the field of microwave technology have made it convenient for chemists to safely attain higher values of temperature and pressure in a short period of time. Understanding its benefits and potential scope in near future, we decided to use microwaves as our principal source of energy employing CEM Microwave synthesizer discover module for focused synthesis (Figure 1).



Figure 1: CEM Microwave synthesizer discover module.

Chemicals and solvents

All chemicals were purchased from Alfa Aesar, Spectrochem and Aldrich chemicals Co. and were used without further purification.

Microwave

CEM microwave synthesizer Discover module, mono-mode microwave reactor was used as the source of microwave energy.

Thin layer chromatography

The adsorbent used for TLC was silica gel GF-254 procured from Merck (India Ltd.). Visualisation of the spot was carried out in UV chamber.

Column chromatography

Column chromatography was performed using 100-200 mesh size using n-Hexane: Ethyl acetate system.

¹H NMR and ¹³C NMR

NMR data (¹H, ¹³C) were recorded on Varian 300 MHz spectrometer in the solvents indicated; chemical shifts are given in ppm.

IR spectroscopy

IR was performed on an FTIR spectrometer from Shimadzu-prestige 21.

All conversions and yields are rounded up to the nearest significant value. The isolated compounds are in their purest form as determined by ¹H NMR (300 MHz).

General procedure

Preparation of 1-tosyl-6,7-dihydro-1H-indol-4(5H)-one(2)

To a solution of 1,5,6,7-Tetrahydro-4H-indol-4-one (1) (500 mg, 3.7 mmol, 1 equiv) in dichloromethane (10 mL) was tetrabutyl ammonium bromide (20 mg) and potassium hydroxide (500 mg) and water 0.5 mL. To the resulting suspension was added p-Toluenesulfonyl chloride (TsCl) (833 mg, 4.3 mmol, 1.18 equiv) slowly for 3 to 4 hours at room temperature. After completion of the reaction as monitored by TLC. Water 3-4 mL was added to the reaction mixture, stir well and separate the layers. The aqueous layer was again extracted with dichloromethane. Combined dichloromethane layers were evaporated to dryness on rotary evaporator. The crude material thus obtained was crystallized

from Toluene to afford 1-tosyl-6,7-dihydro-1H-indol-4(5H)-one as a light pink solid 900 mg Yield= 84%. Mp: 133-135°C. IR (KBr, cm^{-1}): 2962 (m, C-H stretch of $> \text{CH}_2$), 1668 (s, C=O stretch), 1445.39 (s, Ar-C-C skeletal vibration), 1375 (s, S=O stretch and/or C-N stretch), 812.84 (m, Ar-C-H out of plane deformation). $^1\text{H-NMR}$ (300 MHz, ppm): 2.057-2.141 (m, 2H, $-\text{CH}_2$), 2.401-2.444 (m, 5H, $-\text{CH}_2$ and $-\text{CH}_3$), 2.949-2.990 (t, 2H, $-\text{CH}_2$), 6.612-6.624 (d, 1H, Ar-H), 7.238-7.270 (m, 1H, Ar-H), 7.344-7.371 (d, 2H, Ar-H)

Preparation of 5-bromo-1-tosyl-6,7-dihydro-1H-indol-4(5H)-one(3)

Add Cupric Bromide(CuBr_2) (172 mg, 0.76 mmol, 1.5 equiv) to 1-tosyl-6,7-dihydro-1H-indol-4(5H)-one (2) (150 mg, 0.52 mmol, 1 equiv) in ethyl acetate (5 mL) in a 10 mL seal Tube. Place the seal tube in the cavity of CEM Microwave synthesizer in a closed vessel mode and irradiate the reaction mixture using following parameters.

Temperature	Pressure	Power	Time
80°C	10PSI	50W	3 mins.

Table a

After 3 mins of microwave irradiation add 60 mg of CuBr_2 to the reaction mixture in two lots. After adding each lot (30mg each) of CuBr_2 the reaction mixture is irradiated for 1 min using the above parameters under CEM Microwave synthesizer. After completion of the reaction distil out the solvent completely under vacuum. Add 5mL dichloromethane to the concentrated mass and heat 40°C and then filter the mixture. Repeat this dichloromethane addition to the residue and heating to 40°C followed by filtration. Combined dichloromethane layers are washed with water and the solvent is evaporated completely. Finally, Toluene 3 mL is added to the product heated to 50°C, chilled and filtered to give the desired product 5-bromo-1-tosyl-6,7-dihydro-1H-indol-4(5H)-one as white solid 174 mg Yield ~ 91% m.p. 152°C - 154°C. IR (KBr, cm^{-1}): 2890.77 (w, C-H stretch of $> \text{CH}_2$), 1673.91 (s, C=O stretch), 1450.21 (s, Ar-C-C skeletal vibration), 1387.53 (s, S=O stretch). $^1\text{H-NMR}$ (300 MHz, ppm): 2.418-2.469 (t, 5H, $-\text{CH}_2$ and CH_3), 2.989-3.204 (m, 2H, CH_2), 4.489-4.516 (t, 1H, $-\text{CHBr}$), 6.651-6.662 (d, 1H Ar-H), 7.273-7.285 (d, 1H, Ar-H), 7.363-7.390 (dd, 2H, Ar-H), 7.759-7.786 (dd, 2H, Ar-H)

Preparation of 1-tosyl-1H-indol-4-ol(4)

Take 5-bromo-1-tosyl-6,7-dihydro-1H-indol-4(5H)-one (3) (200 mg, 0.543 mmol, 1 equiv), Lithium chloride (24 mg, 0.57

mmol, 1.05 equiv) and Lithium carbonate (44 mg, 0.597 mmol, 1.1 equiv) in dimethyl formamide 4 mL in a 10 mL seal tube and purge with nitrogen gas before closing the lid. Irradiate this mixture with microwaves using following settings in CEM Microwave synthesizer.

Temperature	Pressure	Power	Time
130°C	10PSI	100W	3 mins. (1 min x 3)

Table b

After completion of reaction the inorganics are removed by filtration and subsequent DMF washings. To the combined DMF solution containing the product is added water 25 mL and extracted with toluene (10 mL x 2). Combined Toluene layer is extracted with 5% NaOH solution twice to extract the desired product in the form of a sodium salt in the aqueous solution which on neutralization with hydrochloric acid, filtration and washing with water and drying results in 1-tosyl-1H-indol-4-ol weighing 138 mg yield ~89% m.p. 143°C-146°C. IR (KBr, cm^{-1}): 3454.85 (s, O-H stretch), 2923.56 and 2961.16 (w, C-H stretch of $-\text{CH}_3$), 1440.56 and 1593.88 (m, Ar-C-C skeletal vibration), 1360.53 (s, S=O stretch), 1121.4 (s, C-O stretch and O-H deformation of Ar-OH), 800.314 (s, C-H out of plane deformation). $^1\text{H-NMR}$ (300 MHz, ppm): 2.254 (s, 3H, $-\text{CH}_3$), 5.485 (broad s, 1H, $-\text{OH}$), 6.528-6.565 (d, 1H, Ar-H), 6.669-6.681 (d, 1H, Ar-H), 7.033-7.186 (m, 3H Ar-H), 7.399-7.411 (d, 1H, Ar-H), 7.473-7.501 (d, 1H, Ar-H), 7.665-7.692 (d, 2H, Ar-H).

Preparation of 1H-indol-4-ol (5)

A mixture of sodium hydroxide (350 mg) and water (3 mL) is heated in 10 mL seal tube in CEM Microwave synthesizer for 30 sec at 50°C. To this hot solution is added 1-tosyl-1H-indol-4-ol (4) 250 mg and heat the reaction mixture using 70W power at 90°C for 2 mins under high stirring. Cool the reaction mixture to 10°C and acidify with hydrochloric acid. Add sodium chloride to this mixture and extract with 10 mL ethyl acetate twice washed with water and evaporated the ethyl acetate layer under vacuum below 50°C to give 106mg of 1H-indol-4-ol. Yield ~92% m.p. 93°C-97°C. $^1\text{H-NMR}$ (300 MHz, ppm): 5.137 (br s, 1H, $-\text{OH}$), 6.521 (d, 1H, Ar-H), 6.600 (Unresolved d, 1H, Ar-H), 7.052 (m, 3H, Ar-H) 8.166 (br s, 1H, $-\text{NH}$). $^1\text{H-NMR}$ (300 MHz, ppm): 98.981 (1H, Ar-C), 104.393 (1H, Ar-C), 104.454 (1H, Ar-C), 117.729 (1H, Ar-C), 123.124 (1H, Ar-C), 123.247 (1H, Ar-C), 149.168 (1H, Ar-C).

Preparation of 4-(oxiran-2-ylmethoxy)-1H-indole(6)

In a round bottom flask take water (8 mL), sodium hydroxide(NaOH) (250 mg, 6.25 mmol, 2.7 equiv) and 1H-indol-4-ol (5) (300 mg, 2.25 mmol, 1 equiv). add epichlorohydrin (0.8 mL, 10 mmol, 4.5 equiv) under stirring at room temperature. Stir the reaction mixture at room temperature for 7-8 hours. After complete consumption of 4-hydroxy Indole, as monitored by TLC, charge Toluene (10 mL). Stir the reaction mixture for 15 min. Separate the layers and extract the aqueous layer with Toluene (5 mL x 2). Combines Toluene layer washed with water and evaporated to dryness under vacuum to 320 mg (Yield ~75%) of 4-(oxiran-2-ylmethoxy)-1H-indole. M.p. 63°C.

Procedures for the preparation of the related substances (Impurities) of the active Pharmaceutical substance Pindolol.

Preparation of 3-((1H-indol-4-yl)oxy)propane-1,2-diol (Impurity D of Pindolol)(7)

Take 1H-indol-4-ol (5)(250 mg, 1.88 mmol, 1 equiv) and potassium carbonate (1.3g, 10 mmol, 5.4 equiv) in 5 mL Acetonitrile in a 10 mL sealed tube and irradiate it the CEM Microwave synthesizer for 1 min at 80°C. Then add 3-chloro-1,2-propanediol (0.2 mL, 2.4 mmol, 1.2 equiv) in the reaction mixture and irradiate it with following parameters.

Temperature	Pressure	Power	Time
80°C	20PSI	70W	5 mins. x 3

Table c

After total 15 mins of microwave irradiation the reaction mixture is cooled to room temperature, filtered and the filtrate is concentrated under vacuum to give solid which on column chromatography with 30%-60% Ethyl acetate in Hexane gave 315 mg of the desired product 3-((1H-indol-4-yl)oxy)propane-1,2-diol. Yield = 80% m.p. 94°C-96°C. ¹HNMR (300 MHz, ppm): 3.536 (d, 2H, -CH₂), 3.932 (m, 2H, CH₂), 4.066 (m, 1H, -CH-OH), 4.699 (t, 1H, OH), 4.975 (d, 1H, OH), 6.473 (d, 1H, Ar-H), 6.969 (t, 2H, Ar-H), 7.202 (s, 1H, Ar-H), 11.034 (s, 1H, -NH). ¹³CNMR (75 MHz, ppm): 62.963, 96.447, 70.167, 98.525, 99.920, 104.795, 118.453, 121.779, 123.404, 137.368, 152.206.

Preparation of 1-((1H-indol-4-yl)oxy)-3-chloropropan-2-ol (Impurity F)(8): A solution of 150 mg (0.81 mmol) of 4-(oxiran-

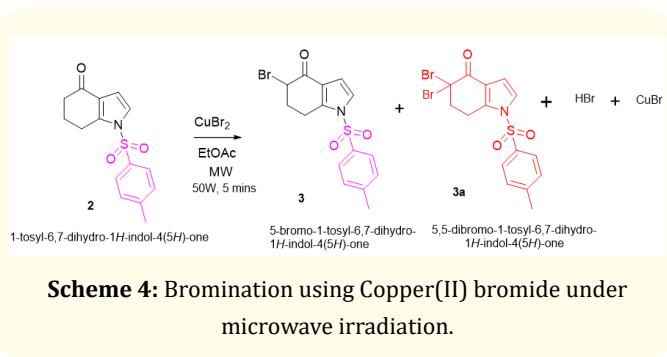
2-ylmethoxy)-1H-indole (6) in 3 mL of dichloromethane, 2 mL of concentrated HCl was added. The reaction mixture was irradiated under CEM microwave synthesizer for 2 mins at 40°C with power of 25W. Then, the product thus formed was extracted with dichloromethane (3 x 5 mL) the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using dichloromethane as eluent. The 1-((1H-indol-4-yl)oxy)-3-chloropropan-2-ol was obtained with an overall yield of 81% (145 mg). ¹HNMR (300 MHz, ppm): 2.734 (d, 1H, OH), 3.799 (m, 2H, CH₂), 4.274 (m, 3H, CH₂ and -CH-OH), 6.533 (d, 1H, Ar-H), 6.627 (d, 1H, Ar-H), 7.076 (m, 3H, Ar-H), 8.221 (br s, 1H, NH). ¹³CNMR (75 MHz, CDCl₃, in ppm): 46.358, 68.876, 70.240, 99.794, 101.235, 105.420, 118.878

Results and Discussion

Herein we report an energy efficient and rapid synthesis of 4-hydroxy indole, a key intermediate for the preparation of Pindolol. As depicted in the reaction scheme above, compound 1 i.e. 1,5,6,7-Tetrahydro-4H-indol-4-one is reacted at room temperature under stirring with p-toluenesulphonyl chloride under basic condition in a biphasic medium of DCM-water using TBABr as the phase transfer catalyst to give the tosylated product 2 quantitatively.

In the next step 1-Tosyl-6,7-dihydro-1H-indol-4(5H)-one 2 is brominated using Cupric bromide (CuBr₂) as brominating agent in ethyl acetate as solvent under CEM microwave synthesizer. In the initial feasibility experiments based on the literature the ratios of keto compound: CuBr₂ is taken as 1: 2. After a few trials it was found that a power of 50 W and temperature of 80°C is sufficient for bromination to take place. However, the reaction is sluggish at the end and much better results were obtained when cupric bromide is added in lots which also enables release of hydrogen bromide gas from the reaction every time we open the tube for cupric bromide addition. It is noticed that during this bromination step there are chances of dibrominated compound (5,5-dibromo-1-tosyl-6,7-dihydro-1H-indol-4(5H)-one) 3a as one of the unwanted products formed if a large excess of CuBr₂ is used. We have deliberately prepared this by-product by adopting similar reaction condition, but excess of cupric bromide (4 equivalent) and the material characterized for confirmation (Scheme 4).

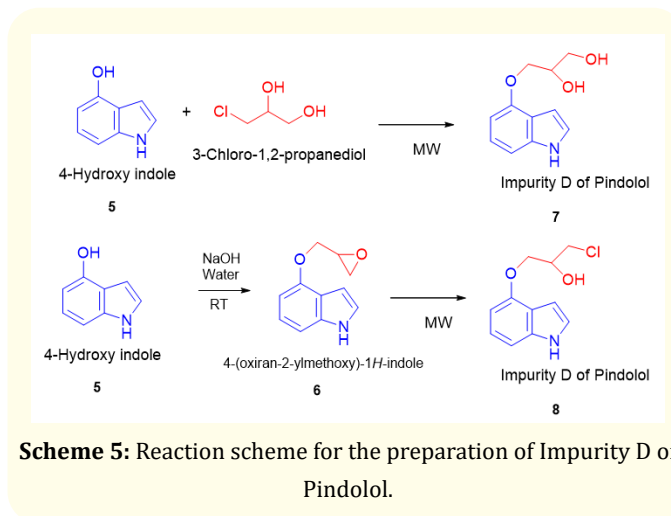
Further the most important step of dehydrohalogenation is achieved using Lithium chloride and Lithium carbonate in DMF



as solvent. This aromatization took place efficiently under focused microwaves of CEM synthesizer at 130°C against 150°C required by conventional method. The yields of both the steps i.e. bromination (91%) and dehydrogenative aromatization (89%) indicates one more applicability of microwave assisted reaction giving rapidly the desired output saving precious time needed for screening of different parameters. The next step is a deprotection reaction under aqueous alkaline conditions to remove the *p*-toluene sulphonyl group attached to the Nitrogen atom of the indole moiety to get the target molecule 4-Hydroxy indole 5 in excellent yield (92%). This pharmaceutically important intermediate serves as a key structure for the building of Pindolol molecule as shown in the reaction scheme above by methods well known in the literature.

Further to extend the scope of the microwave technology in Pharmaceutical industry, we have shown its application in the preparation of related substances (impurities) of the active pharmaceutical substance. After a few optimization reactions using a different base like aqueous potassium hydroxide, Triethyl amine in Ethanol and potassium carbonate in Acetonitrile we found that reaction using the combination of potassium carbonate in Acetonitrile was the best in terms of yield and ease of work up. This is accomplished by reacting 4-Hydroxy indole 5 with 3-chloro-1,2-propanediol in Acetonitrile solvent in presence of potassium carbonate as a base under CEM microwave synthesizer for a total of 15 mins given in the form of 3 cycles of 5 mins each at 80°C.

In another attempt to synthesize 1-((1H-indol-4-yl)oxy)-3-chloropropan-2-ol (Impurity F), first epichlorohydrin was condensed with 4-Hydroxy indole in a facile manner at room temperature under aqueous medium in presence of sodium hydroxide as a base, a method well known in prior art to



No.	Reagent	Solvent	Time (mins)	Conversion
1	Potassium hydroxide	Water	20	38
2	Sodium hydroxide,	Water: Ethanol (1:1)	18	48
3	Triethylamine	Ethanol	20	62
4	Potassium carbonate	Acetonitrile	15	80

Table 1: Screening experiments for synthesis of impurity D to find a combination of alkali and solvent which gives desired conversion rapidly in minimum time span.

give 4-(oxiran-2-ylmethoxy)-1H-indole. Further hydrolysis accomplished with ring opening of the 3-membered oxiran moiety was carried out efficiently under acidic conditions by applying a power of 25W for 2 mins with 40°C as reaction temperature in fewer attempts to easily give the target Impurity F of Pindolol in good yields (81%). Here the desired product was isolated in its purest form by column chromatography and all the compound is synthesized were characterized using necessary techniques like m.p., IR, ¹HNMR, ¹³CNMR detail procedure is given below in section of 'Methods'.

Conclusion

Using the CEM microwave synthesizer, an energy-efficient technique for the synthesis of pharmacologically and commercially important intermediate 4-Hydroxy indole (used for synthesis of

Pindolol) from their corresponding 4-Oxo indole was established in a closed vessel to obtain the target molecule with good yields in a very quick reaction time. The formation of the products was confirmed by m.p., IR, and NMR methods. This approach may be applied for the performing a variety of dehydrogenative aromatization reaction. Scope of microwave radiation in the preparation of the related substance of the active pharmaceutical ingredient (only few milligrams of impurities required for analytical purpose) by conducting feasibility experiments in short period of time was established which has promising future in pharmaceutical industry, as use of microwaves helps research and development departments to conclude about the feasibility of the reaction in short period of time and thereby increase the productivity.

Acknowledgements

We acknowledge the Head of the Department of Ramnarain Ruia autonomous College for providing the necessary support to conduct research at the institution. We acknowledge Centaur Pharma for providing the support for IR and NMR analysis.

Conflict of Interest

The authors declare no conflict of interest.

Bibliography

1. AP Taylor, *et al.* "Modern advances in heterocyclic chemistry in drug discovery". *Organic and Biomolecular Chemistry* 14 (2016): 6611-6637.
2. R Tandon, *et al.* "Recent Advances and Developments of *in vitro* Evaluation of Heterocyclic Moieties on Cancer Cell Lines". *Chemical Record* 19 (2019): 362.
3. D Garella, *et al.* "Microwave-assisted synthesis of N-heterocycles in medicinal chemistry". *MedChemComm* 4 (2013): 1323-1343.
4. N Chadha and O Silakari: "Indoles as therapeutics of interest in medicinal chemistry: Bird's eye view". *European Journal of Medicinal Chemistry* 134 (2016): 159-184.
5. P Bamfield and PF Gordon. "Aromatic benzene compounds from acyclic precursors". *Chemical Society Reviews* 13 (1984): 441.
6. M Hayashi. "Oxidation using activated carbon and molecular oxygen system". *Chemical Record* 8 (2008): 252.
7. H Z Liu, *et al.* "Selective phenol hydrogenation to cyclohexanone over a dual supported Pd-Lewis acid catalyst". *Science* 326 (2009): 1250.
8. M T Musser. "Ullmann's Encyclopedia". *Ind Chem* 203 (2011): 1889.
9. SA Girard, *et al.* "Catalytic dehydrogenative aromatization: an alternative route to functionalized arenes". *Organic Chemistry Frontiers* 2 (2015): 279.
10. A Skita and H Ritter. "Über die Sabatiersche Reduktion und ihre Umkehrung". *European Journal of Inorganic Chemistry* 44 (1911): 668.
11. P Sabatier. "Hydrogénations et déshydrogénations par catalyse". *European Journal of Inorganic Chemistry* 44 (1911): 1984.
12. HC Chitwood, *et al.* "Phenols by Dehydrogenation". *Industrial and Engineering Chemistry Research* 44 (1952): 1696.
13. D Walker and J D Hiebert. "2,3-Dichloro-5,6-dicyanobenzoquinone and Its Reactions". *Chemical Review* 67 (1967): 153.
14. Y B Zhou, *et al.* "Ratiometric Visualization of NO/H₂S Cross-Talk in Living Cells and Tissues Using a Nitroxyl-Responsive Two-Photon Fluorescence Probe". *Annals of Chemistry* 89 (2017): 4587.
15. Xueli Liu, *et al.* "Catalytic dehydrogenative aromatization of cyclohexanones and cyclohexenones". *Organic and Biomolecular Chemistry* 16 (2018): 8662.
16. Claas Hundsdörfer, *et al.* "Indeno[1,2-b]indole derivatives as a novel class of potent human protein kinase CK2 inhibitors". *Bioorganic and Medicinal Chemistry* 20.7 (2012): 2282-2289.
17. Michael J Zacuto and Dongwei Cai. "α-Hydroxylation of carbonyls using iodine". *Tetrahedron Letters* 46.3 (2005): 447-450.
18. Eric D Edstrom, *et al.* "Regioselective oxidation of 2,3,5,6,7,8-hexahydro-8-oxo-1H-pyrrolo [1,2-α]indoles. Useful intermediates for the synthesis of mitosenes". *Tetrahedron Letters* 36.39 (1995): 7035-7038.
19. "Method for synthesizing 4-hydroxyindole using 1,3-cyclohexanedione". Chinese patent CN113321609.

20. Soederberg Bjoern C., *et al.* "Synthesis of indoles by palladium-catalyzed reductive n-heteroannulation of 2-nitrostyrenes: methyl indole-4-carboxylate". *Organic Syntheses* 80 (2003): 75-84.
21. Julia Marc and Pascal Yves R. "Indoles". XXII. New synthesis of the indole nucleus". *Chimica Therapeutica* 5.4 (1970): 279-284.
22. "Preparation of 4-hydroxyindoles". Japanese patent JP04208262.
23. Tanaka Hideo., *et al.* "A Facile Synthesis of 4-Hydroxy- and 4-Aminoindoles through Corresponding Indolines". *Bulletin of the Chemical Society of Japan* 62.11 (1989): 3742-3744.
24. Somei Masanori., *et al.* "The Chemistry of Indoles. XVI. A Convenient Synthesis of Substituted Indoles carrying a Hydroxy Group, a Halogeno Group, or a Carbon Side Chain at the 4-Position via 4-Indolediazonium Salts and a Total Synthesis of (±)-6, 7-Secoagroclavine". *Chemical and Pharmaceutical Bulletin* 29.11 (1981): 3145-3157.