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SYNTHESIS OF BIFONAZOLE MICROWAVE IRRADIATION VS. CONVENTIONAL METHOD

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Abstract

A convenient and cost effective synthetic process has been developed for the synthesis of an anti fungal drug bifonazole. The process involves of three steps: the first step being the Friedle-Craft alkylation of biphenyl to 4-phenyl-benzophenone with benzoyl chloride in the presence of $AlCl_3$, the second step being the reduction of 4-phenyl-benzophenone to biphenyl-phenyl-carbinol being with sodium borohydride in the presence of alumina, and the third step being the reaction between biphenyl-phenyl-carbinol and imidazole carried out by conventional and microwave (*in the absence of any organic or inorganic solvents*) condition offered. In conclusion, the conventional method required 15 hours while microwave assisted synthesis required 30 minutes for reaction with high yield.

Keywords: Bifonazole, Anti-fungal drug, Microwave Irradiation, Green Chemistry.

Introduction:

Microwave-assisted organic reactions have been applied as a useful technique in organic synthesis [1,2]. Microwave irradiation often leads to shorter reaction times, increased yields, easier workup and matches with green chemistry protocols. Furthermore, its unique capabilities allow its application in reactions which are difficult or impossible to carry out by means of conventional methods[3,4]. Bifonazole is, a new broad-spectrum antimycotic imidazole antifungal drug. Bifonazole has dual mode of action - it blocks transformation of 24-methylendihydrolanosterole to desmethylsterol in fungi together with inhibition of HMG-CoA. Conventional synthesis of bifonazole reported in the various literatures [5,6,7,8].

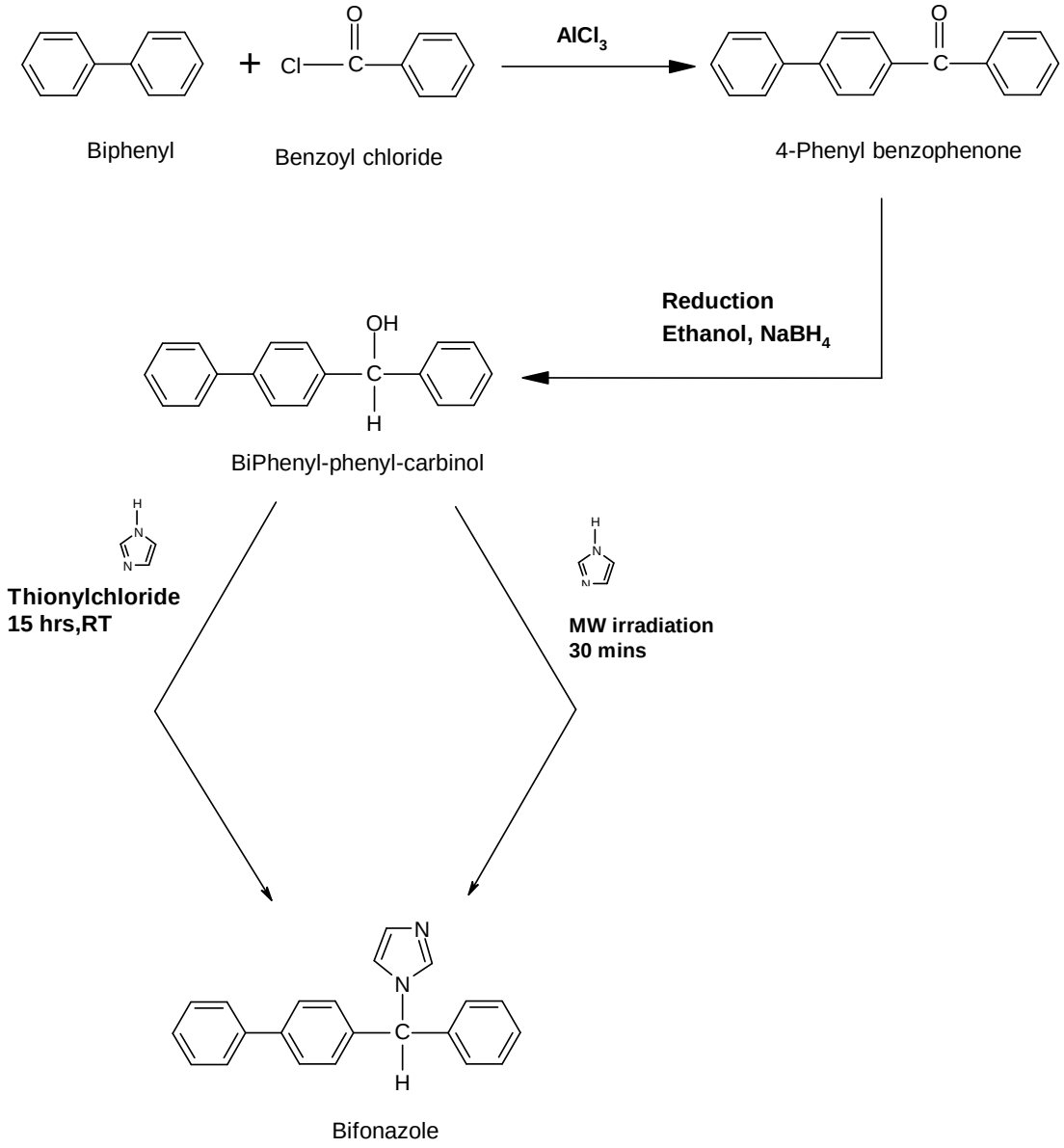
(1) The German Patent 3,538,873 (1987) describes a method of synthesis for Bifonazole; reacting 4-benzoylbiphenyl with imidazole in a 1:4 molar relation in p-$CH_3C_6H_4SO_3H$; heating the system at 180 degrees Celsius; then adding formic acid dropwise during five hours. A mixture of water-formic acid is distilled at the end of the reaction. Bifonazole is obtained in a 72.3% yield in relation to the theoretical.

(2) Bifonazole has also been prepared by benzoylation of imidazole with PhCOCl, yielding 74.7% of 1-benzoylimidazole which is subject to react with Gringnard's reactant 4-PhC_6H_4MgBr followed by a tosylation and subsequent reduction with sodium cyanoborohydride in hexamethylphosphoramide, to yield 68.2% Bifonazole (Es. Patent 539,345). So on application of microwave technology in organic

synthesis in this study synthesis for Bifonazole comprises of three steps: the first step being the Friedle-Craft alkylation of biphenyl to 4-phenyl-benzophenone with benzoyl chloride in the presence of $AlCl_3$, the second step being the reduction of 4-phenyl-benzophenone to biphenyl-phenyl-carbinol being with sodium borohydride in the presence of alumina, and the third step being the reaction between biphenyl-phenyl-carbinol and imidazole carried out by conventional and microwave (*in the absence of any organic or inorganic solvents*) condition separately to the bifonazole **(Scheme-I)**.

EXPERIMENTAL WORK

Yield reported here are un-optimized. The melting points (m.p.) were determined using a Tosnniwal melting point apparatus (heating block type) and are uncorrected. The IR spectra were recorded using the KBr disc method on an FT- IR model 8300 (Shimadzu, Japan). The ^1H NMR spectra on a 300 MHz spectrometer (Brucker, USA) were recorded in a $CDCl_3$ (chemical shift in δ ppm). Microwave synthesis was carried out in microwave oven (Sharp ,Carousel).

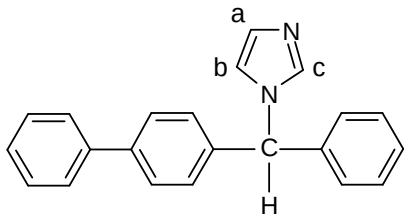


Scheme-I Synthetic scheme of bifonazole

Synthesis of 4-phenyl-benzophenone: The benzoyl chloride (1mole) was taken in to a pressure equalizing dropping funnel containing carbon disulfide (10ml) and added slowly to a stirred mixture of biphenyl (1 mole), anhydrous aluminium chloride (1.5mole) and carbon disulfide (5 ml) at a temperature below 20 °C over a period of 10 minutes under anhydrous condition. After complete addition the reaction mixture was further stirred for 15 minutes at a room temperature and then refluxed for 1 hr. The reaction mixture was poured onto crushed ice containing conc. HCl (10 ml) and extracted with chloroform (150 ml). The combined organic was washed with sodium bicarbonate solution followed by washing with water, dried and chloroform recovered. The residue was recrystallized in methanol to give the desired compound as white precipitate. (Yield 95 %), m.p. 95 °C, IR (KBr, cm^{-1}): 1685 (C=O streching).

Synthesis of biphenyl-phenyl-carbinol : 4- phenylbenzophenone (3.82×10^{-2} mole) was supported by chemisorbtion in 10 g of alumina using 20 ml ethanol until forming a paste (slightly humid), to which 1.5 g of sodium borohydride (3.92×10^{-2} mole) is added. The reaction mixture is stirred for 40 minutes at room temperature. The reaction mixture was poured onto acidulated water at pH1 to hydrolyze excess of borohydride. The alumina was filtered and the filtrate was left to crystallize to obtain desired compound as white precipitate. (Yield 89 %), m.p. 125 °C, IR (KBr, cm^{-1}): 3215 (-OH streching).

Synthesis of bifonazole:



Bifonazole

Conventional method: A mixture of imidazole (14.5×10^{-4} mole), thionyl chloride (10ml) and acetonitrile (5 ml) as solvent was stirred at 10° C. To the resulting thionylbisimidazole solution, biphenyl-phenyl-carbinol (19.5×10^{-4} mole) of was added in a 1:4 molar relation. After fifteen hours at room temperature, the solvent was removed by vacuum distillation. The remaining was dissolved in chloroform and washed with water, the organic phase was dried over sodium sulfate, filtered and the solvent was vacuum distilled. The resulting solid was purified by recrystallization in acetonitrile to give the desired compound as white precipitate. (Yield 50 %), m.p. 145 °C, IR (KBr, $cm^{-}1$): 1262 (C-N), 1517 (C=N), PMR: δ 7.12-7.50 (m, 14H, Ar-H), 6.6 (s, 1aH), 6.7 (s, 1bH), 6.9 (s, 1cH) and 1.6 (s, 1H3°)

Microwave method: (19.5×10^{-4} mole) of biphenyl-phenyl-carbinol was mixed with imidazole (7.96×10^{-4} mole) in absence of solvent, placed in a sealed container, which was placed in a microwave oven. The sample was irradiated during 30 minutes at 40 power. The residue was recrystallized in acetonitrile to give the desired compound as white precipitate. (Yield 75 %), m.p. 145 °C, IR (KBr, cm^{-1}): 1265 (C-N), 1525 (C=N), PMR: δ 7.12-7.50 (m, 14H, Ar-H), 6.6 (s, 1aH), 6.7 (s, 1bH), 6.9 (s, 1cH) and 1.6 (s, 1H3°). Elem.anal. ($C_{22}H_{18}N_2$): Calculated % → C-85.13, H-5.85, N-9.03 and Found % → C-85.23, H-5.79, N-9.05.

Conclusion:

In this study a convenient method over conventional method was devised during microwave. The bifonazole was synthesized using both conventional and microwave method.The conventional method required **15 hours** while microwave assisted synthesis required **30 minutes** for reaction.High yield in

microwave irradiation about 75% as compared to conventional method (50 %). The environment is not contaminated by using reactants such as thionyl chloride because microwave synthesis was carried out in absence of solvent.

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