

SYNTHESIS OF ANTICANCER DRUG ANASTROZOLE VIA PHASE-TRANSFER CATALYST

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Abstract

2, 2'-[5-(1H-1, 2, 4-triazol-1-ylmethyl)-1, 3-phenylene] bis (2-methylpropanenitrile) (anastrozole) is a novel non-steroidal drug exhibiting the inhibitory action of the enzyme aromatase which is currently used for the treatment of advanced breast cancer in post menopausal women. Herein we introduce an effective method in synthesis of the drugs using phase-transfer catalyst (PTC). In the same condition, the yield of anastrozole increased in the order of DMF < toluene + benzakonium chloride (BKC) < toluene + tetrabutyl ammonium bromide (TBAB). Moreover, use of PTC in the reaction issued a highly selective method and high yield, resulting in reduction of isomeric impurity of anastrozole in the obtained product.

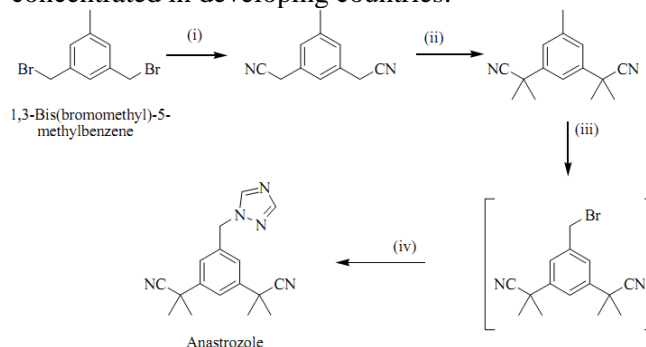
Keywords. Anastrozole anticancer drug, phase-transfer catalyst.

1. INTRODUCTION

In Vietnam, annually, the number of diagnosed cancer cases was approximately 150,000 and breast cancer is the most frequently diagnosed [1]. The cost of importing new cancer drugs is an economic burden for every developing country in general, and for Vietnam particularly. Therefore, domestic production of the new drugs is very significant to reduce the cost of importing new drugs and improve cancer treatment methods.

For breast cancer cases in women, the majority of breast tumors are found to be hormone-dependent, with estrogens playing a key role in the growth and development of the disease. This has led to the development of endocrine therapies to remove the influence of estrogen on breast cancer cells [2]. In Vietnam hospitals, the current strategy involves blocking the receptors of cancer cell which will catch estrogen using tamoxifen. However, the drug may cause the risk of blood clots or endometrial cancer in some women [3]. A new approach in developed countries concentrated on restricting the availability of estrogens by interfering with its biosynthetic pathway via inhibition of the enzyme (e.g. aromatase) with anastrozole. Several clinical studies with anastrozole showed improved efficacies and superior toxicity profiles when compared to tamoxifen [4, 5].

Anastrozole is a non-steroidal and expensive drug marketed under the trade name Arimidex. Exclusive patent for preparation of the drug came off patent in 2011 (as shown in scheme 1) [2]. Studies on preparation of the drugs have been concentrated in developing countries.



Scheme 1: Synthetic process of anastrozole

However, order of precursor chemicals for the synthetic process is unavailable and uneconomic. Moreover, in the final reaction it is difficult to obtain high purity of anastrozole due to production of its isomeric impurity and high yield of anastrozole.

To overcome these challenges, we expanded the current process in which the first precursor (1,3-bis(bromomethyl)-5-methylbenzene) was synthesized from mesitylene (other precursors were sequentially obtained following the current process,

data not shown here) and the anastrozole was obtained from alkylation reaction of 1,2,4-triazole sodium salt and a bromide-containing precursor was conducted in presence of phase-transfer catalyst (scheme 2).

2. EXPERIMENTAL

2.1. Materials

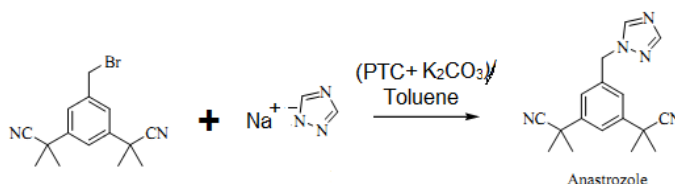
1,2,4-triazole sodium salt, tetrabutyl ammonium bromide and benzakonium chloride (benzyl dimethyl dodecyl ammonium chloride, ~60 % benzyl dimethyl tetradecyl ammonium chloride, ~40 %) were purchased from Sigma Aldrich. 3, 5-bis (2-cyanoprop-2-yl)benzyl bromide was prepared at Materials and Pharmaceutical Chemical Laboratory-Institute of Applied Materials Science. Dimethyl formamide (DMF) and toluene were purchased from Shanghai Chemical Co., China.

2.2. Preparation of anastrozole in absence or presence of PTC

3,5-Bis (1-cyano-1-methyl) bromomethyl benzene (0.3 g, 0.001 mol), 1,2,4-triazole sodium

(0.18 g, 0.002 mol), K_2CO_3 (1 g) and 2 ml DMF were added to round flask (100 mL) then heating at 90 °C for 5 hours. After finishing the reaction, 20 ml H_2O was added to the mixture and then extracted 3 times with 15 ml ethyl acetate. Organic layer was collected then dried with $MgSO_4$ and concentrated for column chromatography. Impure anastrozole was obtained by column chromatography (isopropyl alcohol and heptane). Higher purity of anastrozole could be obtained by crystallization with cosolvent (isopropyl alcohol and heptane).

In presence of phase-transferred catalyst (PTC) (scheme 2), TBAB or BKC (0.1 g) was added to the mixed reagents and toluene (5 ml). The mixture was heated at 90 °C for 5 hours. Anastrozole was obtained by removal of toluene under vacuum and column chromatography (isopropyl alcohol and heptane). Melting point is 77-81 °C. The anastrozole structure was characterized by 1H , ^{13}C NMR (500 MHz, $CDCl_3$): δ 1.73 (12H, H-9,10,13,14), 5.40 (2H, t, H-15), 7.34 (2H, d, $J = 1.5$ Hz, H-2,6), 7.54 (1H, t, $J = 1.5$ Hz, H-4), 8.01 (1H, s, H-17) and 8.16 (1H, s, H-16). δ_H (270MHz, $CDCl_3$), 29.04 (C-9,10,13,14), 37.27 (C-7,11), 53.04 (C-15), 122.12 (C-4), 123.86 (C-3,5), 124.03 (C-2,6), 136.88 (C-8,12) 143.28 (C-1), 143.456 (C-16) and 152.499 (C-17).



Scheme 2: Synthesis of anastrozole in presence of Phase-transferred catalytic

2.3. Characterizations

Structure of anastrozole was analyzed using 1H NMR measured by BRUKER AVANCE 500 NMR Spectrometer at 500 MHz and ^{13}C NMR measured by 125 MHz.

3. RESULTS AND DISCUSSION

3.1. Anastrozole structure and purity

Anastrozole is generally prepared via alkylation reaction with corresponding benzyl bromide derivative and 1,2,4-triazole or its salt. In the generally synthetic scheme, the obtained anastrozole's purity is replied on a separately chemical shift of protons 16 and 17 (shown in Figure 1), which indicates that the sample has no isomeric impurity, because the isomeric impurity would cause the peak 16 and 17 overlap each other [6].

Moreover, the typical peaks of anastrozole protons appeared with corresponding ratios of integral.

Results of LC-MS analysis revealed that anastrozole exhibited molecular ion at m/z (M+H) 294 amu.

3.2. Effect of phase-transfer catalyst on the synthesis

Phase transfer catalysis is a powerful tool improving process efficiency and product selectivity in organic chemical reactions. In comparison with conventional methods, PTC holds considerable advantages in terms of cost (which avoids expensive anhydrous dipolar aprotic solvents), time, mildness, and simplicity. Small quantity of PTC extracts one of the reactants, most commonly an anion, across the interface into the other phase where reaction can take place with the substrate and reaction can proceed. These PTC may be a quaternary ammonium salt for example a tetraalkyl ammonium

halide, or crown ether. The alkyl group is an alkyl of 1 to 18 carbon atoms. Preferably, the alkyl is methyl, ethyl or propyl. In the study, we evaluated effect of PTC on the synthesis of anastrozole. Figure 3 shows that use of small amount of TBAB and BKC could significantly improve yield of anastrozole.

Use of DMF as solvent was expected to improve the synthetic yield in comparison with toluene because the solvent is highly polar that could improve solubility of triazol sodium salt. But the actual yield of anastrozole synthesized in toluene appeared to be the lowest. This could be explained from the loss of anastrozole in water phase during ethyl acetate extraction. In the presence of PTC, the obtained yield significantly increased. In comparison with BKC at the same condition, TBAB gave higher yield. In general, quaternary salts having 10-30

carbon atoms are usually suitable for PTC. Cations containing one long alkyl chain and methyl groups are poor catalysts, because they tend to form micelles and stay in the aqueous phase [7]. So BKC structure possesses the above character that could limit triazolyl anion transfer capability a crossing the interface (solid-liquid) into the liquid phase for alkylation. Quaternary salts possessing all butyl groups (TBAB) have superior anion transfer capability [7], resulting in a higher yield of the reaction. Moreover, in a phase transfer reaction, using of an inorganic salt (K_2CO_3) in the aqueous phase enable to improve phase transfer by salting out (reducing the degree of hydration) the phase transferring (anion) [7]. Understanding characters of PTC could issue an efficient synthetic method with high product selectivity in synthesis of drugs.

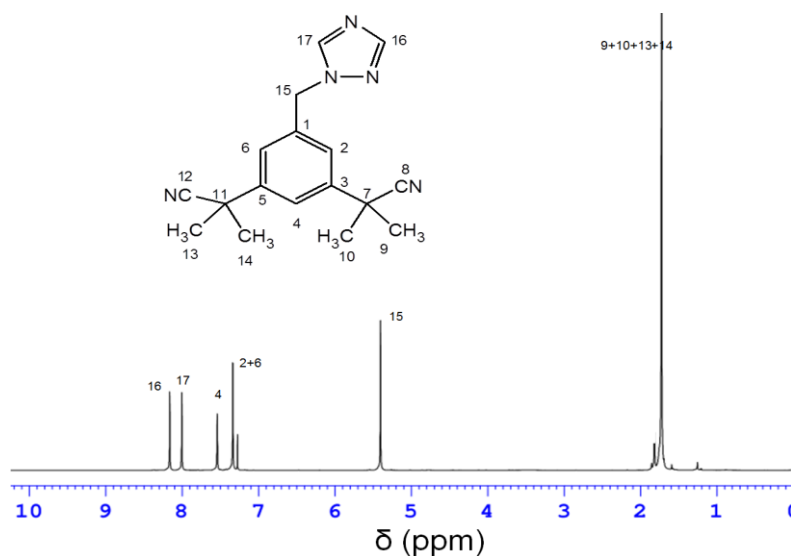


Figure 1: 1H NMR spectrum of anastrozole

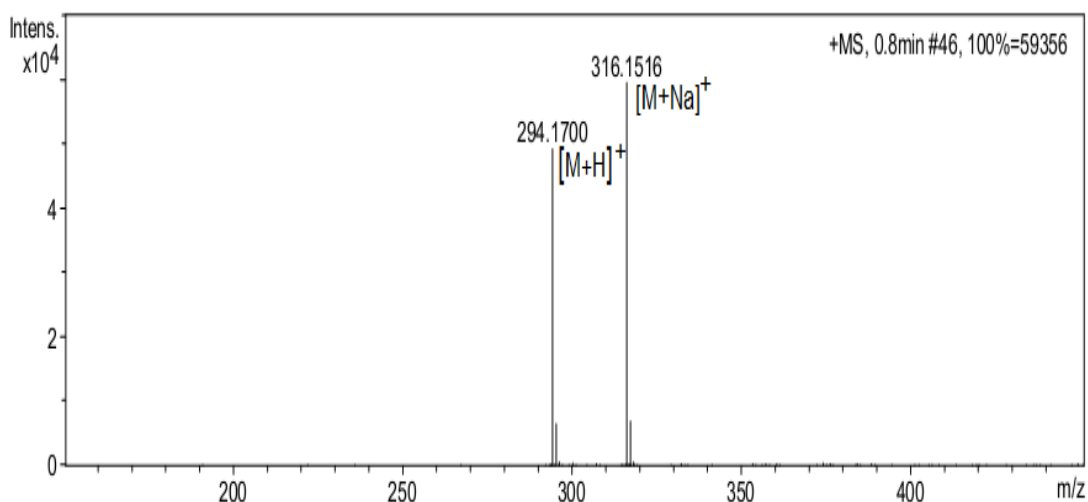


Figure 2: LC/MS of anastrozole

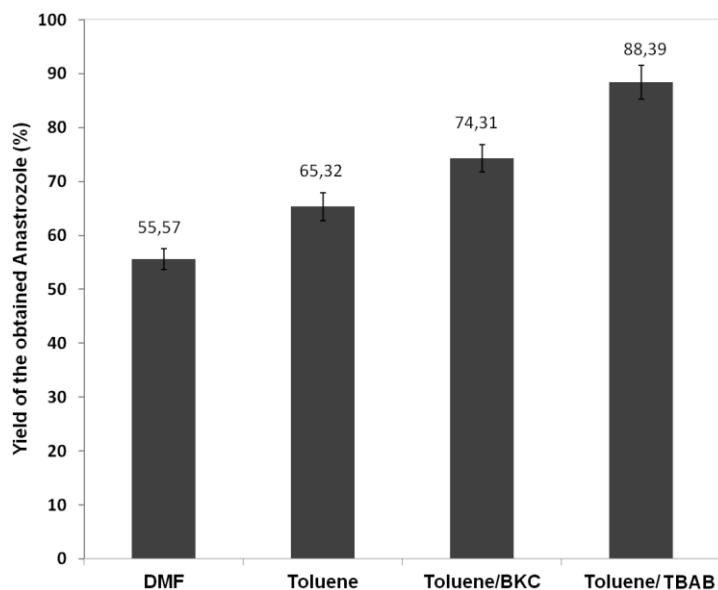


Figure 3: Effect of solvents and PTC on the obtained yield of anastrozole

4. CONCLUSION

In the study we investigated the yield of anastrozole prepared with different solvents and phase-transfer catalyst. The obtained results showed the best efficiency in presence of TBAB and toluene solvent. Success in this work may pave a new direction for producing anastrozole in Vietnam. This may be very significant to reduce the cost of importing new drugs and improve the treatment method for cancer patients in Vietnam.

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