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Green chemical approach towords Irbesartan synthesis

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ABSTRACT

Use of solid supported reagents like gel entrapped base catalyst (GEBC), sodium azide supported on alumina & Pd acetate on Hydrotalcite for synthesis of Irbesartan. The major advantage is low cost, moderate reaction conditions and minimum waste with no hazards to environment. Includes recycling of all used reagents with no waste at all.

KEYWORDS

Irbesartan;
GEBC;
Sodium azide on alumina;
Pd acetate on hydrotalcite.

INTRODUCTION

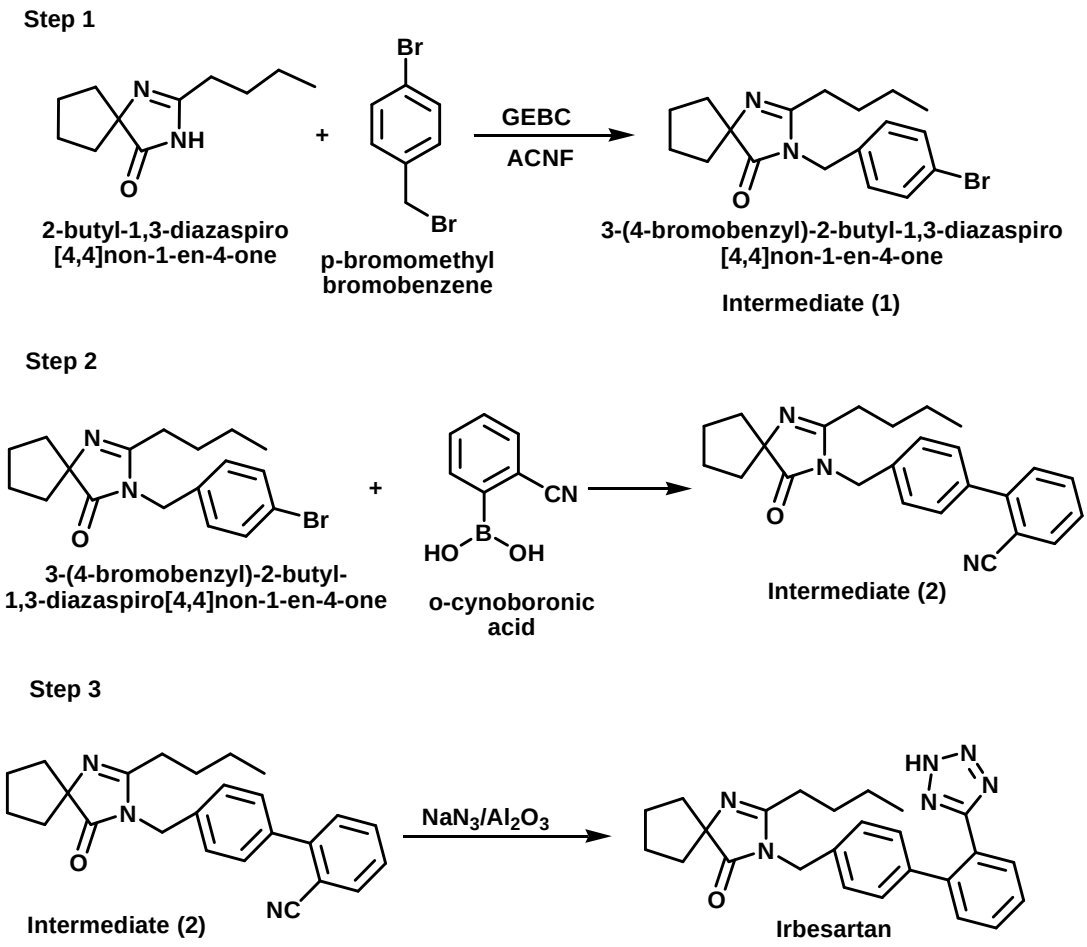
Herewith introduced novel method for synthesis of Irbesartan[1]. Irbesartan is an angiotensin drug used as anti cholesterol. Number of methods for synthesis of Irbesartan have been reported[2-7]. The traditional method has major drawback of messy workup and lot of waste. The reaction conditions are also very harsh causing lot of side reactions in turns giving impure substances with fewer yields. Generation of impurities during reaction requires extra added purification method. Here we include solid supported reagents like GEBC[8], sodium azide on alumina[9,10] and Palladium acetate on Hydrotalcite[11-14].

All the reagents and intermediate used here are commercially available. The process discussed is also commercially viable. The major advantage of this process is its low cost. The tradition method uses harsh conditions which causes impurity formation in all steps. So extra purification need to be added to purify the material. By using this method we can increase the yield from10-15%. All the reagents used here can be recycled adding impact of overall 5-10%. So overall cost can be reduced up to 20-25% by using solid supported route. Here also introduced catalyst for Suzuki coupling reaction i.e. Palladium acetate supported on Hydrotalcite. The use of Hydrotalcite supported catalyst gives 100% recovery along with very neat and clean reaction. Isolation of catalyst from reaction mixture is also very easy just by filtration. Also the problem associated with heavy metals and sulphated ash by using palladium also minimized. Conversion by using palladium acetate on Hydrotalcite is also improved.

REACTION SCHEME

First step of reaction

In first step diazo compound reacts with p-bromomethylbromo benzene to form intermediate (I). The traditional method involves the use of aq. solution of sodium hydroxide or potassium hydroxide, water immiscible organic solvent and phase transfer catalyst. Under these conditions there is possibility of hydrolysis of C=N to give open chain impurity. Reaction by using



Scheme 1

GEBC involves single solvent system i.e. polar water miscible or water immiscible organic solvent. Due to absence of aq. base impurity formation is negligible. Rate of reaction is also increased and can be done at moderate conditions. To avoid the deterioration of base formed by acid during course of reaction it is advisable to use equivalents of base. For the reaction 20% sodium hydroxide in GEBC is used. Both the starting materials are commercially available. It is found that rate of reaction is much faster in water in water miscible organic solvent than that of water immiscible.

Second step of reaction

Involves the Suzuki coupling of o-cynoboronic acid with intermediate (1). Traditional method involves use of palladium in presence of triphenyl phosphine. Major drawback of this reaction is isolation of last traces of ligand and metal which also associated with slow reaction and no. of byproducts. Reaction by using palladium acetate on Hydrotalcite is comparatively fast and very clean. Hydrotalcite support can be easily removed from reaction mixture by filtration and phosphine by aqueous washings. Yields are quantitative by using this method. It is found that reaction is fast in toluene which takes around 8-10 hrs as compared to that of palladium which takes 15 hrs. Conversion is >90% as that of 75% by palladium.

Third step of reaction

The final step of reaction is tetrazole formation. The traditional method involves the use of sodium azide tributyl tin chloride, in presence of phase transfer catalyst. Completion of reaction requires refluxing in these conditions for 12-24 hrs. Major drawback of the above said method is tedious workup and risky reaction conditions which can be very hazardous. Here introducing new catalyst sodium azide supported on alumina. By using alumina supported sodium azide there is no need of phase transfer catalyst and time of reaction can be reduced from 24 to 10hrs. We can separate azide just

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TABLE 1

Sr. No.	Solvent	Time (Hrs)	Yield (%)	NaOH loading on catalyst
1	Dichloromethane	4.2	92	30 %
2	Chloroform	4.0	90	30 %
3	Acetonitrile	3.0	94	20%
4	Tetrahydrofuran	3.0	93	20%

by filtration. It is easy to use sodium azide supported on alumina reducing risk factor. Also the simple work up avoids the yield loss. Sodium azide can be supported on alumina up to 30%. Dissolving sodium azide in water followed by addition of alumina which on subsequent drying at 55-60°C to remove moisture give sodium azide supported on alumina.

EXPERIMENTAL

Synthesis of intermediate (1)

The equimolar mixture of bromomethylbromobenzene and free base of diazaspiro compound stirred in Acetonitrile. Then to it added GEBC (1T). Reaction mass stirred at room temperature till completion. To avoid deterioration of GEBC 1 equivalent of organic base is added. After completion of reaction GEBC filtered, solvent distilled out. Product crystallized from diisopropyl ether. Overall 94% isolated yield.

Here all the solvents and catalyst used can be recycled. The above said method can be repeated with water immiscible solvents like chloroform and methylene dichloride. In all above solvents isolated yield more than 90%. ^{1}HNMR: δ ppm 0.89-0.91 (t, 3H); 1.25-1.35 (m, 4H); 1.49-1.53 (t, 2H); 1.55-1.61 (m, 8H); 5.21 (s, 2H); 7.10-7.12 (d, 2H); 7.78-7.81 (d, 2H).

Synthesis of intermediate (2)

Equimolar mixtures of intermediate o-cynoboronic acid and **(1)** treated with 5% palladium acetate on Hydrotalcite in toluene with potassium carbonate as base. The reaction mixture is refluxed till completion of reaction. It is advisable to use close system which gives faster reaction. After completion of reaction catalyst removed by filtration, followed by distillation of toluene and crystallization from ether gives intermediate **(2)**. Isolated yield observed to be more than 90%. Filtered catalyst died and reused. It was found that there is no loss in activity up to 10 cycles.

For the screening of base different bases were tried but the best results were obtained with potassium carbonate other give poor conversion. ^{1}HNMR: δ ppm 0.89-0.91 (t, 3H); 1.25-1.35 (m, 4H); 1.49-1.53 (t, 2H); 1.55-1.61 (m, 8H); 5.21 (s, 2H); 7.65-7.81 (m, 4H).

Synthesis of Irbesartan

Equimolar mixtures of intermediate **(2)**, sodium azide supported on alumina (1.5 eq), tributyl tin chloride (1 eq), heated in toluene at 90-100°C. After completion of reaction cooled to room temperature catalyst removed by filtration. Product extracted in 2 N Hydrochloric acid at 50-55°C. Cooled pH adjusted to 4.9-5.1 by 10% sodium hydroxide to get the solid. Filter the solid and purify by using ethanol. ^{1}HNMR: δ ppm 0.89-0.91 (t, 3H); 1.25-1.35 (m, 4H); 1.49-1.53 (t, 2H); 1.55-1.61 (m, 8H); 5.21 (s, 2H); 7.45-7.81 (m, 8H).

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