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Williamson Ether Synthesis: O-Alkylation Reaction Using Halogenated Hydrocarbons as Alkylating Agents

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Abstract: *The Williamson synthesis method is a method for preparing asymmetric ethers, which is obtained by the reaction of halogenated hydrocarbons with sodium alcohol or sodium phenol. According to literature research, the influencing factors of this reaction include halogenated hydrocarbons, alkylated alcohols, catalysts, solvents, and side reactions; In addition, this method can be used to introduce various substituents such as saturated, unsaturated, aliphatic, and aromatic hydrocarbon groups in drug synthesis, thereby obtaining a variety of pharmaceutical intermediates or drugs. This article selects the antitumor drug gefitinib involved in this reaction as a case study to illustrate the complete synthesis route of this drug. Other reaction types and names involved in the drug synthesis route are also described.*

Keywords: *Williamson ether synthesis method; influencing factors; application of drug synthesis; synthesis route; route exploration and analysis*

1. Introduction

Different alkyl carbon chains, the active type of halogenated hydrocarbon RX decreases with the increase of alkyl carbon chain. Therefore, in order to introduce long carbon chain alkyl groups, brominated alkanes need to be used as alkylating agents, while iodinated alkanes are mostly used for laboratory preparation due to their high cost.

1.1 Factors affecting the synthesis of Williamson ether

1.1.1 Effects of halogenated hydrocarbon RX [1]

1.1.1.1 Same as alkyl R

The greater the polarization of the C-X bond, the faster the reaction rate, so R-I>R-Br>R-Cl.

1.1.1.2 Same as halogen X

Types of carbon positive ions, in Williamson synthesis, only primary haloalkanes and sodium alcohols can be selected as raw materials. Because sodium alcohol is both a nucleophilic reagent and a strong base, secondary and tertiary haloalkanes (especially tertiary haloalkanes) mainly undergo elimination reactions to generate olefins under strong base conditions.

Low activity of haloaromatic hydrocarbons, due to the conjugation of halogenated aromatic hydrocarbons with aromatic rings, their activity is low and they are not prone to react. Therefore, for Ar-O-R ethers, ArOH+RX is used instead of ArX+ROH. However, when there are electroactive groups in the ortho and para positions of halogenated aromatic rings, the reaction can proceed smoothly.

1.1.2 Affected by hydrocarbon ROH [2]

For the alkylated alcohols, if the activity of ROH is weak, it is necessary to use alkaline substances in the reaction to form nucleophilic RO negative ions.

1.1.2.1 Acidity of the hydrocarbon ROH

Alcohols are alkyl alcohols (weak acidity of hydroxyl groups), generally, they are strong bases, such as NaH, KH, LDA, LHMDS, NaHMDS, etc;

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Alcohol is a phenolic hydroxyl group (strongly acidic hydroxyl group), weak Lewis bases such as Na_2CO_3 and K_2CO_3 can be used;

Special reactions, metal such as Na and K can be directly used for hydrogen replacement to prepare alcohol negative ions.

1.1.2.2 Activity of alkylating agent

When reacting with halogenated hydrocarbons with low activity, an appropriate amount of potassium iodide is usually added to replace them with iodinated hydrocarbons to increase their reaction activity, and then the alkylation reaction with the low activity hydrocarbonated substance ROH is carried out. The general dosage of potassium iodide is from 1/10 mol to 1/5 mol. The hydrogen atom activity of the hydrocarbonated substance ROH varies, and the conditions for the hydrocarbonation reaction vary.

1.1.3 Effect of catalyst

In general reactions, sodium alcohol is added, and sometimes Na, NaH, NaOH, and KOH are added. Organic bases such as (i-Pr) $_2$ NEt, DMA (N, N-dimethylaniline), HMPA (hexamethylphosphoramide), etc. can also be added.

1.1.4 Effects of solvents

1.1.4.1 Protonic solvent

Although protonic solvents are beneficial for the dissociation of R-CH $_2$ - X, the solvation reaction with RO negative ions will reduce the nucleophilic activity of RO negative ions.

Proton polar solvents such as ethanol are prone to elimination reactions of certain halogenated hydrocarbons.

Generally, excess alcohol can be used to add sodium to make RONa, and then halogenated hydrocarbon RX can be added.

1.1.4.2 Non proton solvent

Non proton solvents such as benzene, toluene (Tol), xylene (Xyl), dimethyl sulfoxide (DMSO), and N, N-dimethylformamide (DMF) can be selected and used under anhydrous conditions.

1.1.5 Effects of side effects

1.1.5.1 Elimination reaction

Tertiary halogenated hydrocarbons have a SN process and are prone to elimination reactions under strong alkaline conditions. Therefore, the reaction should be carried out under neutral or weak alkaline conditions. (Sodium tertiary alcohol is difficult to form and is not easy to react with halogenated hydrocarbons after formation, so tertiary halogenated hydrocarbons are often used to prepare ethers under weakly alkaline conditions.) [3]

1.1.5.2 Racemization

Benzyl halogenated hydrocarbons undergo an SN process, forming carbon positive ions and RO negative ions that react in two different directions to form racemized products. (Benzyl alcohol has high activity and is commonly used to prepare aryl ethers)

1.2 Application of Williamson ether synthesis method in drug synthesis [4]

In drug synthesis, Williamson ether synthesis can be used to introduce various substituents such as saturated, unsaturated, aliphatic, and aromatic hydrocarbon groups, thereby obtaining a variety of pharmaceutical intermediates or drugs.

1.2.1 Diphenhydramine, an antihistamine [5]

Two synthesis methods can be used:

The first method is due to β- The activity of hydroxyl groups in dimethylaminoethanol is low, so it is necessary to first treat it with strong alkali to convert it into alkoxy anion for alkylation reaction; The second method increases the hydrogen atom activity of the hydroxyl group due to the electron absorption effect of the two phenyls of diphenyl methanol. Therefore, the alkylation reaction can be carried out by adding sodium hydroxide or the like as a deacidifying agent in the reaction.

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1.2.2 Hypolipidemic drug - Gemfibrozil

Using toluene as solvent and potassium iodide as catalyst.It is obtained by the alkylation reaction of 2-methylpropyl dimethyl valerate.

1.2.3 Antipsychotic drug Aripiprazole

Using 7-hydroxy-3, 4-dihydro-2 - (1H) - quinolinone as the starting material, the hydroxy group undergoes an O-alkylation reaction with 1, 4-dibromobutane to produce 7 - (4-bromobutyloxy) - 3,4-dihydro-2 - (1H) - quinolinone, which is then obtained by N-alkylation with 1 - (2,3-dichlorophenyl) piperazine under the catalysis of Nal.

1.2.4 Paeonol, an antipyretic, analgesic, and anti-inflammatory drug [6]

When a carbonyl group exists in the ortho position of a phenolic hydroxyl group, intramolecular hydrogen bonds can easily be formed between the carbonyl group and the hydroxyl group to passivate the phenolic hydroxyl group, allowing other free hydroxyl groups to undergo alkylation reactions. For example, when 2, 4-dihydroxyacetophenone is methylated with iodomethane, the 4-methoxy product paeonol is obtained instead of the o-methoxy product.

1.2.5 Antibacterial drug - Sulfamethoxypyrazine

"Nitrogen-containing heterocyclic compounds such as pyridine, pyrimidine, pyridazine, and quinoline, if the halogen atom is located in the ortho or para position of the nitrogen atom, also have increased activity, and can undergo alkylation reactions with alcohols to obtain corresponding pyroxy products." For example, sulfamethoxypyrazinum is prepared by reacting 3-sulfamethoxypyrazine with methanol in the presence of sodium hydroxide, and then undergoing acidification.

1.2.6 Antitumor drug Geftinib

Using 6-hydroxy-7-methoxy-3H-quinazoline-4-one as the raw material, the phenolic hydroxyl group is first protected, and then the corresponding chlorinated product is obtained through a chlorine substitution reaction with $SOCl_2$. Under the action of copper salts, the corresponding chlorinated product is subjected to a UImann reaction with 3-chloro-4-fluoroaniline, and through alkaline hydrolysis, 4 - (3-chloro-4-fluoroaniline) - 6-hydroxy-7-methoxyquinazoline is generated. Finally, the target product is obtained through a 0-alkylation reaction with chloropropylmorpholine or bromopropymorpholine.

1.2.7 Phenyl o-nitrophenyl ether, an intermediate of Nimesulide, an anti-inflammatory and analgesic drug

Using o-nitrochlorobenzene and phenol as raw materials, an Ullman reaction takes place under the action of Cu and KOH to produce diaryl ether, which is the intermediate of Nimesulide, phenyl o-nitrophenyl ether.

1.2.8 Intermediate of peptide hormone Thyroxine

Using 3,4,5-triiodo nitrobenzene and p-methoxyphenol as raw materials.

Under action, Ullman reaction occurs, producing an intermediate of the peptide hormone thyroxine.

1.2.9 Herbicide - Nitrophen

Using p-nitrochlorobenzene and potassium 2,4-dichlorophenol as raw materials, under the action of Cu and KOH ,a Ullman reaction occurs to produce a herbicide, nitrophen. [7]

2. Other reaction types and names involved in the synthesis route of the antitumor drug gefitinib

2.1 First step reaction - acylation reaction (acetic anhydride as acylation reagent)

Using 6-hydroxy-7-methoxy-3H-quinazoline-4-one and acetic anhydride as raw materials, with anhydride as a strong acylating agent, it is commonly used for the acylation of phenolic hydroxyl groups and sterically hindered tertiary alcohols. The reaction is a polarized reaction in which acid anhydride provides acetyl positive ions and 6-hydroxy-7-methoxy-3H-quinazoline-4-one provides alcohol negative ions. Phenol hydroxyl groups are protected by acylation into esters, and then the ester groups are hydrolyzed under alkaline conditions to obtain unreacted alcohol hydroxyl groups.

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2.2 Second step reaction - halogenation reaction (sulfoxide chloride as halogenation reagent)

Firstly, the carbonyl group undergoes enol tautomerism, and $SOCl_2$ serves as a halogenation reagent to provide chloride anion, which undergoes a halogenation reaction with the hydroxyl group to obtain corresponding chlorinated products. In addition, the actual form of $SOCl_2$ reacting in DMF is a chloride imine salt, known as the Vilsmerier Haack reagent, which has high activity and selectivity and effectively combines the generated hydrogen chloride to achieve the effect of chlorine substitution.

2.3 The third step reaction—alkylation reaction (halogenated aromatic hydrocarbons are alkylation reagents)

Under the action of copper salts, a UImann reaction occurs with 3-chloro-4-fluoroaniline. Due to the low activity and steric hindrance of halogenated aromatic hydrocarbons, it is not easy to react with aromatic primary amines. By adding copper or copper iodide and potassium carbonate to co heat, diphenylamine and its homologues can be obtained, achieving N-alkylation. [8]

2.4 Fourth step reaction - hydrolysis reaction (hydrolysis to remove hydroxyl protection groups)

The ester group undergoes a hydrolysis reaction under alkaline conditions to remove the acetyl protection group from the phenolic hydroxyl group, ultimately achieving the goal of protecting the hydroxyl group and ensuring that the hydroxyl group is not reacted during the reaction process. [9]

2.5 Fifth step reaction - alkylation reaction (Williamson ether synthesis method)

Alcohol hydroxyl groups form alcohol negative ions, attack the carbon positive ion center of halogenated hydrocarbons, and ultimately remove the halogen from halogenated hydrocarbons to form ether bonds, which is the Williamson ether synthesis method to achieve O-alkylation. The reaction conditions are alkaline, high concentration of alkali, and high temperature is favorable for the reaction; Moisture is detrimental to the reaction.

3. Summary

In drug synthesis, Williamson ether synthesis can be used to introduce various substituents such as saturated, unsaturated, aliphatic, and aromatic hydrocarbon groups, thereby obtaining a variety of pharmaceutical intermediates or drugs.[10]

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