The comparison of protecting methods to the amino group in 2-Aminomethylphenylacetic acid

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Abstract 2-Aminomethylphenylacetic acid is an important intermediate of ceforanide, and this article compared two different protecting agents for protecting the amino group in 2-aminomethylphenylacetic acid by BOC (Di-tert butyl dicarbonate) or acetacetic ester, and compared the deprotection condition. The yield was higher when BOC was used as protecting agent, but when it was deprotected, it was more difficult than when acetacetic ester was used as protecting agent.

Keywords 2-Aminomethylphenylacetic acid · Ceforanide · Protecting amino group · Deprotect of amino group BOC (Di-tert butyl dicarbonate) · Acetacetic ester

Introduction

Ceforanide is the new cephalosporin developed by the Takeda company [1–4], and 2-Aminomethylphenylacetic acid is an important intermediate of Ceforanide. The amino group must be protected before the carboxyl can condensate with the amino in 7-ACA, and the protected group must be kept stable when the condensation reaction occurs, and then it should be easy removed after the condensation reaction is over.

There are many methods for protecting the amino group[5], but BOC [6, 7] and acetacetic ester [8] are more suitable for protective reagents for 2-aminomethylphenylacetic acid. This article compared two protective agents for protecting the amino group and for deprotection after reaction (Figs. 1, 2).

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NH₂



Fig. 1 BOC as protective agent

Fig. 2 Acetacetic ester as protective agent



Reaction of BOC protective agent

2-Aminomethylphenylacetic acid (20 g, 0.12 mol), 1,4-dioxane (30 ml), and H₂O (15 ml) were added to a three-necked flask, stirred until dissolved, with the temperature kept below 0–5 °C, then BOC (32 g, 0.15 mol) was added, with stirring continued for 10 min, and then was allowed to slowly warm to room temperature, and kept at this temperature for 3 h. The reaction was monitored by TLC (methanol:ethanol = 3:1) until the raw material spot disappeared. The mixture was evaporated in a vacuum to get rid of 1,4-dioxane, extracted with acetic ether, then citric acid was added to the aqueous phase to pH 2–3, The solid which appeared was filtered, washed with 20 ml brine, and dried at 60 °C in a vacuum to obtain a white powder (2-(Boc-aminomethyl)phenylacetic acid); the yield was 88.1 %, m.p. 115–117 °C.

Reaction of acetacetic ester as protective agent

After reaction between sodium (0.60 g, 0.026 mol) and absolute ethanol (50 ml), the mixture was added drop by drop into another mixture of 2-aminomethylphenylacetic acid (4.27 g, 0.03 mol), acetacetic ester (3.38 g, 0.03 mol) and 42 ml absolute ethanol, and refluxed for 6–7 h. After cooling down to room temperature, the mixture was suction filtered and the liquid was evaporated to dry. The solid was recrystallized with absolute ethanol and the production was 6.36 g colorless crystal needles (sodium 0-(1-ethoxycarbonyl-1-propen-2-ylaminomethyl)phenylacetate); the yield was 82.3 %, m.p.: 230–232 °C.

Deprotection of BOC 2-Aminomenthylphenylacetic acid

2-(Boc-aminomethyl)phenylacetic acid (2.65 g, 0.01 mol) and trifluoroacetic acid (TFA) (2.28 g, 0.2 mol) was stirred at room temperature until no further gas was released. Diethyl ether (20 ml) was added into the clear solution and stirred. After the solid came out, the mixture was suction filtered. The solid was washed by diethyl ether and dried in a vacuum. The solid was dissolved in water and 10 % NaOH was added drop by drop into the solution to get white crystals in an ice bath. After suction filtration, the crystals were washed with water and dried in a vacuum to obtain a white solid (2-Aminomethylphenylacetic acid) ,m.p. 180–182 °C, yield 78 %.

Deprotection of acetacetic ester protected 2-amionmethylphenylacetic acid

Sodium 0-(1-ethoxycarbonyl-1-propen-2-ylaminomethyl)phenylacetate (2.99 g, 0.01 mol) was dissolved in water and 4 N HCl was added drop by drop into the solution to pH = 2.0 in an ice bath. After suction filtration, the solid was washed with water and dry in a vacuum, to give a white solid (2-aminomethylphenylacetic acid), m.p. 180–182 °C, yield 79 %.

Result and discussion

The yield is higher when BOC was the protective agent, but the recovery is more difficult for 1,4-dioxane, because of the high boiling point of 1,4-dioxane and the more expensive trifluoroacetic acid (TFA) as deprotective agent; sodium ethoxied had to be used in strict anhydrous condition. Anhydrous ethanol had to be used as solvent, otherwise the yield was too low. Although the yield is lower when using acetacetic ester as protective agent, the cheaper inorganic acid or base can be applied for the deprotected reaction. It is a good choice for us to use acetacetic ester for protecting the amino group.

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