THE NOVEL PREPARATION METHODS OF 5-SUBSTITUTED METHYL-1-AZABICYCLO[3.3.0]OCTANE

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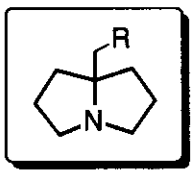
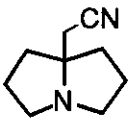
Abstract ----- 5-Substituted methyl-1-azabicyclo[3.3.0]octane, which is a useful intermediate for drugs, was readily synthesized from 1,7-dichloro-4-heptanone without isolating unstable intermediates.

5-Substituted methyl-1-azabicyclo[3.3.0]octane derivatives such as 5-cyanomethyl-1-azabicyclo[3.3.0]octane (**1**) are useful intermediary materials for preparing various medicines [1] since they contain an alkaloid skeleton.



5-Substituted methyl-1-azabicyclo[3.3.0]octane



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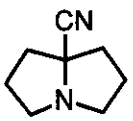

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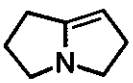

3

The conventional synthetic method [2] of **1** has the following disadvantages : a low overall yield, a high reaction temperature and the handling of the unstable intermediate, 1-azabicyclo[3.3.0]oct-4-ene (**3**). In this paper, we describe the convenient preparation of **1** in which no unstable intermediate is generated.

We have already reported the synthesis of **2** [3] in which the cyano group was introduced to the bridgehead position. We assumed that **2** might be produced by the nucleophilic attack of a cyano anion on the iminium chloride (**4**), which might be formed from 1,7-dichloro-4-heptanone (**5**). Therefore, we planned to prepare **1** *via* nucleophilic attack of the cyanomethyl anion on **4** (Scheme 1). We selected cyanoacetic acid as the

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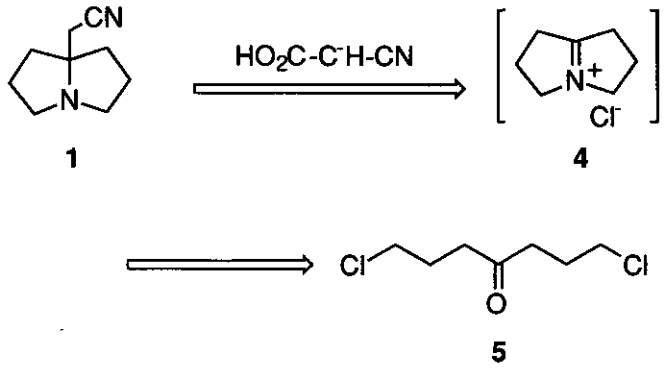
This paper is dedicated to 25th Anniversary of HETEROCYCLES.

cyanomethyl anion source. Because the α-carbon of cyanoacetic acid has a moderate nucleophilicity enough to attack **4**, thus the carboxyl group could be readily removed by decarboxylation.



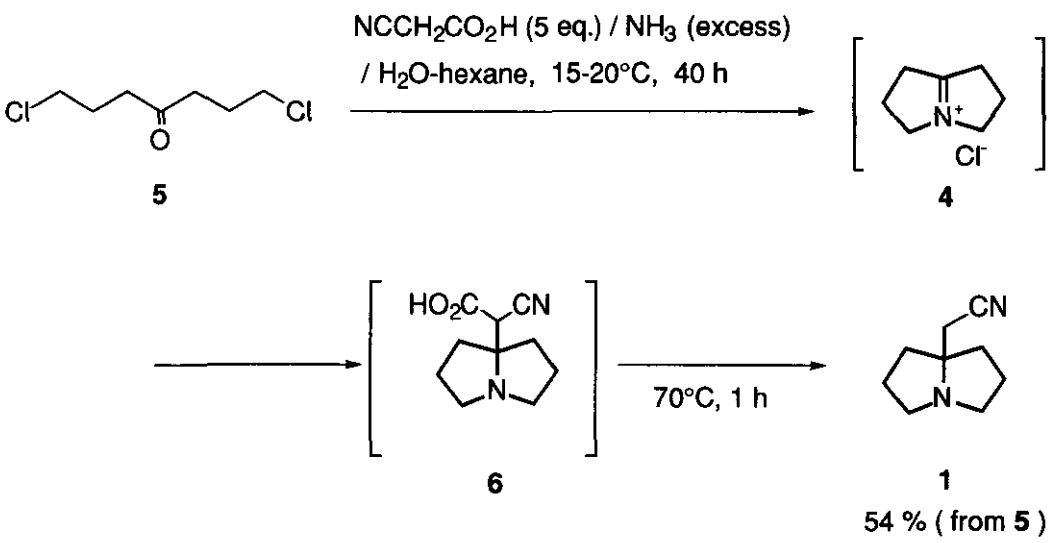
1 **4** **5**

Scheme 1

According to this strategy, the reaction of **5** (1.00 eq.) with cyanoacetic acid (5.00 eq.) and ammonia gave **6**, which was detected by NMR. Next, the reaction mixture was heated for one hour for the decarboxylation to produce **1**.

In this reaction, it appeared that the concentration of ammonia in the reaction mixture had to be maintained as high as possible. The reaction in the mixture of 28% aqueous ammonia solution and hexane did not give **6**. The reaction proceeded in following two cases; one was in a homogeneous MeOH(46 eq.)-H_2O(4 eq.) solution for 16 hours, where H_2O was used to resolve the cyanoacetic acid, and the other was in a heterogeneous H_2O(50 eq.)-hexane(1.4 eq.) solution for 40 hours and hexane was used to resolve **5**. In both reactions, the ammonia saturated solution was freshly prepared with ammonia gas at low temperature (0-5 °C). We considered that these high ammonia concentrations might be required for the dehydration process for the preparation of **4** from **5**, which was discussed in our previous paper [3].

Thus 2.8 g of ammonia gas was bubbled into 7.3 ml of 25 % ammonia aqueous solution at 0 °C, after removal of the bath 1.0 g of 1,7-dichloro-4-heptanone in 1 ml of hexane and 2.3 g of cyanoacetic acid were added at 15 °C to stir for 40 hours. After the hexane layer was removed from the reaction mixture, almost all of the ammonia were removed *in vacuo*, if necessary, water was added, the reaction mixture was stirred for one hour at 70 °C and extracted by ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated to afford 0.45 g of **1** in 54 % yield (from **5**, as shown in Scheme 2).



Scheme 2

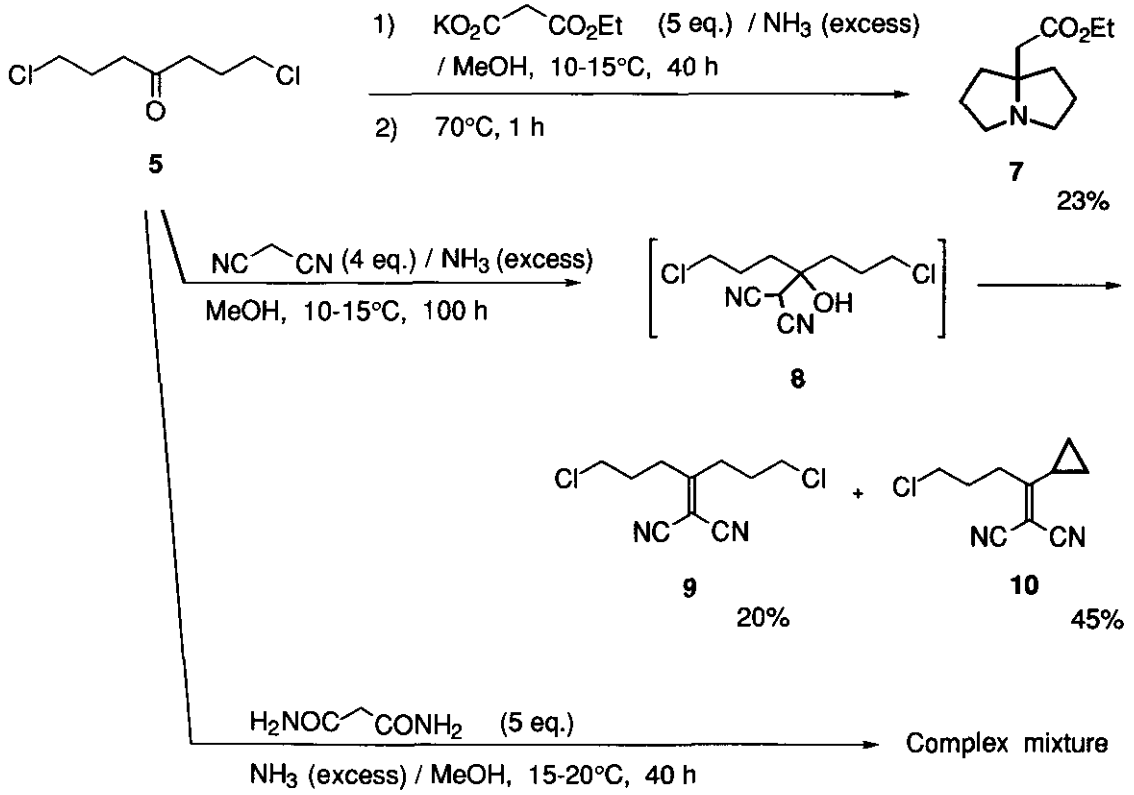
Additionally, we investigated if the above reaction was applied to the malonic acid derivatives having various nucleophilicities at the α carbon (as shown in Scheme 3). Thus the ester (**7**) was produced in 23% yield by the reaction of **5** with ethyl malonate potassium salt, which might have the same nucleophilicity as cyanoacetic acid in MeOH saturated with ammonia at 10 - 15 °C followed by the decarboxylation. In this reaction, a certain amount of **7** might be converted to the amide derivative by the reaction with ammonia.

The reaction of **5** with malononitrile, having a nucleophilicity higher than cyanoacetic acid under the same conditions, gave **9** and **10**. In this reaction, the malononitrile might attack the carbonyl carbon of **5** to give **8**, which was detected by NMR. Because of the high acidic proton between the two cyano groups, **8** might be dehydrated to give **9**. Furthermore, **9** might be cyclized to **10**.

On the other hand, the reaction of **5** with malonamide, having a nucleophilicity lower than cyanoacetic acid, gave a complex mixture which might be polymeric compounds of **3**. We thought that the nucleophilicity of the α carbon in malonamide was too low to attack **4**.

As described above, the scope and limitations of the reaction of **5** with malonic acid derivatives could be established. We thought that these values probably depend upon the pKa value of the proton at the α position in the malonic acid derivatives. Now, we are investigating the reactions of 5 with the other nucleophiles.

We succeeded in the preparation of **1** from **5** with a satisfactory yield for the industrial production using cyanoacetic acid. As the cyano group in **1** could be converted into various functional groups, we are now preparing various kinds of medicines which have the 1-azabicyclo[3.3.0]octane group.



Scheme 3

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