

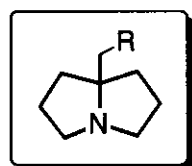
THE NOVEL PREPARATION METHODS OF 5-SUBSTITUTED METHYL-1-AZABICYCLO[3.3.0]OCTANE

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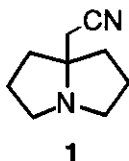
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Abstract ----- 5-Substituted methyl-1-azabicyclo[3.3.0]octane, which is a useful intermediate for drugs, was readily synthesized from 1,7-dichloro-4-heptanone without isolating unstable intermediates.

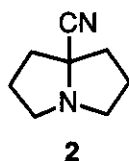
5-Substituted methyl-1-azabicyclo[3.3.0]octane derivatives such as 5-cyanomethyl-1-azabicyclo[3.3.0]octane (**1**) are useful intermediary materials for preparing various medicines ¹ since they contain an alkaloid skeleton.



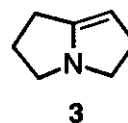
5-Substituted methyl-1-azabicyclo[3.3.0]octane



1



2

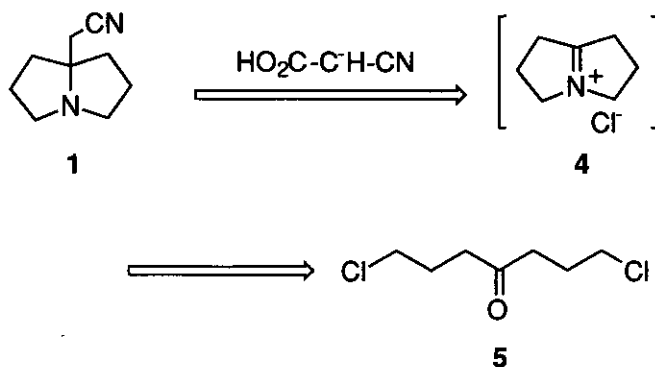


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The conventional synthetic method ² of **1** has the following disadvantages: a low overall yield, a high reaction temperature and the handling of the unstable intermediate, 1-azabicyclo[3.3.0]oct-4-ene (**3**). In this paper, we describe the convenient 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

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.

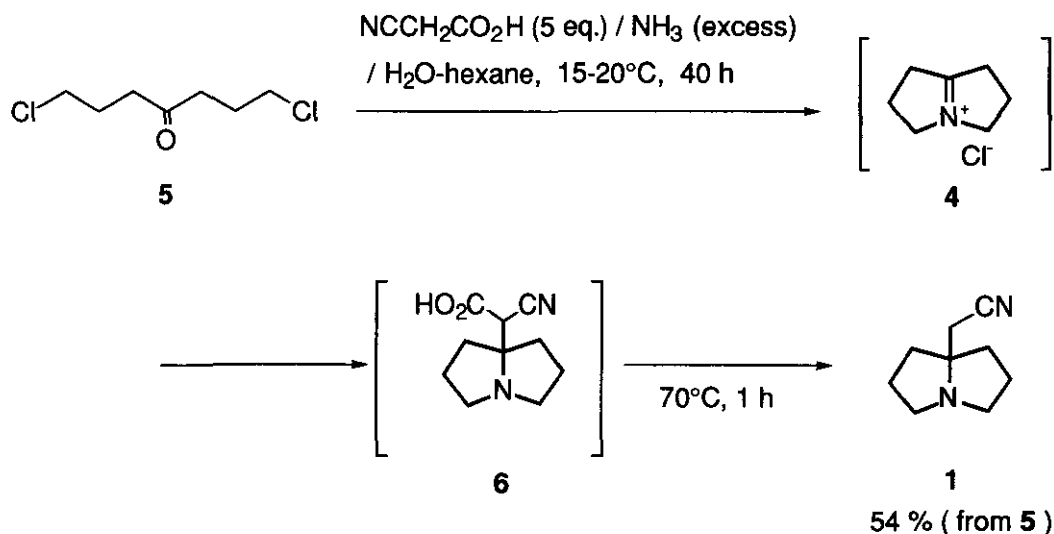


Scheme 1

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.)-H₂O(4 eq.) solution for 16 hours, where H₂O was used to resolve the cyanoacetic acid, and the other was in a heterogeneous H₂O(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 paper³.

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

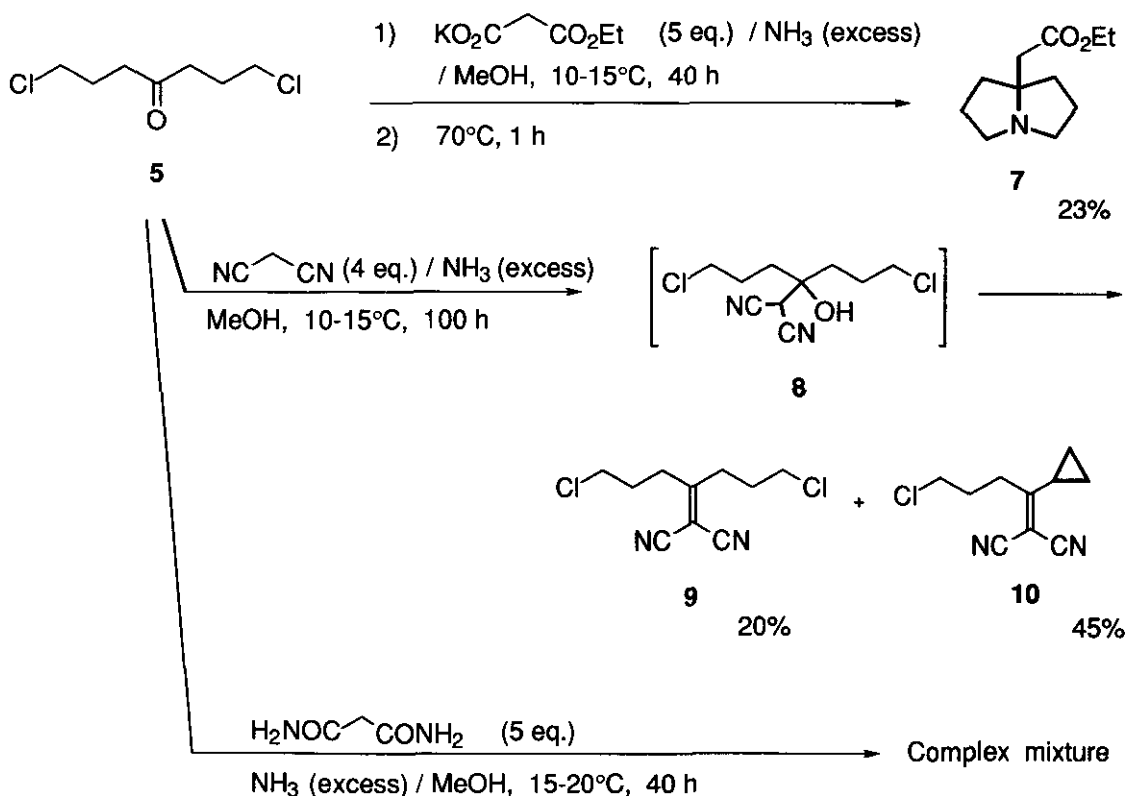
Additionally, we investigated if the above reaction was applied to the malonic acid derivatives having various nucleophilicities at the α carbon (as shown in Scheme 3). Thus the ester (7) was produced in 23% yield by the reaction of 5 with ethyl malonate potassium salt, which might have the same nucleophilicity as cyanoacetic acid in MeOH saturated with ammonia at 10 - 15 $^\circ\text{C}$ 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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