THE NOVEL SYNTHESIS OF 5-CYANO-1-AZABICYCLO[3.3.0]OCTANE

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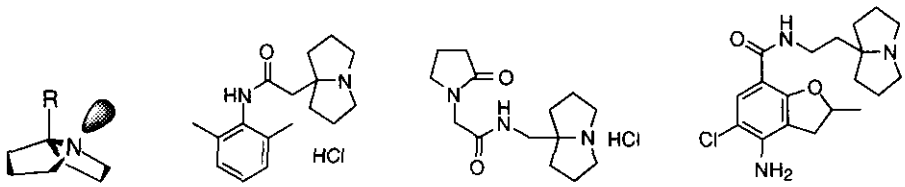
Abstract ------ 5-Cyano-1-azabicyclo[3.3.0]octane (**1**), which is a key intermediary material to some medicines, was prepared from 1,7-dichloroheptan-4-one (**7**) *via* only one step under mild conditions. The reaction mechanism is also discussed.

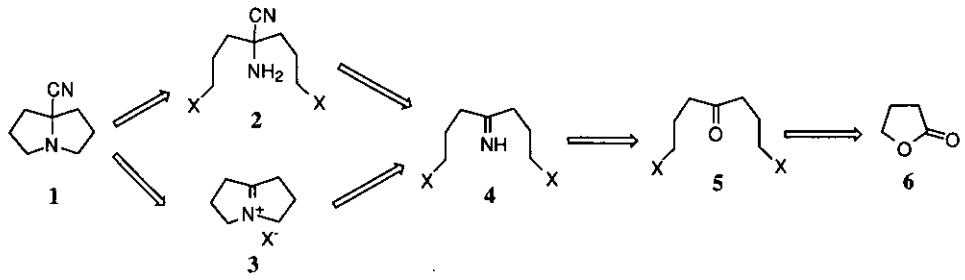
5-Substituted 1-azabicyclo[3.3.0]octane derivatives have a unique structure such that a lone pair on the bridgehead nitrogen is fixed in the same direction as a substituent on the fifth position. Accordingly, any derivatives might be expected to have specific interactions with enzymes or receptors. Recently, they have been used as part of the structure of some drugs.[1] The preparations have been already reported.[2] However, there were some disadvantages such as the low overall yields, the high reaction temperature, and the handling of the metal Na at 90-120°C. In order to supply the 5-substituted 1-azabicyclo[3.3.0]octane derivatives as the raw materials for the drug production, we developed a preparation method with a high yield under mild conditions. In this report, we described the novel synthesis of 5-cyano-1-azabicyclo[3.3.0]octane (**1**), in which the cyano group could be converted into the various functional groups.[3]



Scheme 1 Medicines containing with 1-azabicyclo[3.3.0]octane moiety

We planned the following synthetic strategy according to its retrosynthesis (Scheme 2). At first, the ring opened structure (**2**), which was an intermediate in the Strecker reaction could be postulated. From **2**, it could be transformed to **4**, and then to the ketone (**5**). As another route, the compound (**3**), which had the cyano group removed from **2**, and its opened form (**4**), could be postulated. Compound (**5**)(X=Cl) [4] has been reported to be synthesized from γ-bu-

tyrolactone (**6**).



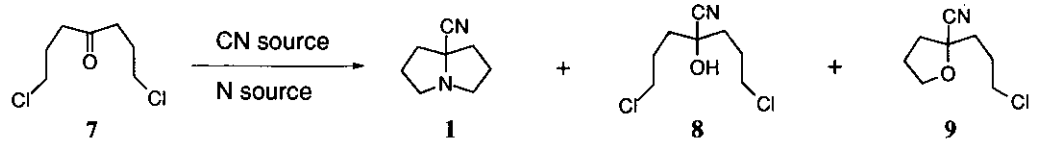
Scheme 2 The retrosynthesis of 5-cyano-1-azabicyclo[3.3.0]octane (**1**)

According to these strategies, we tried to develop a synthetic route from **7** [4] (Table I). At first, **7** reacted under the Strecker reaction conditions, i.e., **7** was reacted with KCN, NH_4Cl, and aqueous NH_3 in a mixture of H_2O-MeOH to give **1**, the by-products (**8**) and (**9**), and the starting material (**7**) in the mole ratio of 14:22:42:22 (run 1). Although some experiments were done under different conditions such as the various mole ratios among the reagents, reaction temperature, and reaction time, we could not selectively obtain only **1** in any case.

Table I Preparations of 5-Cyano-1-azabicyclo[3.3.0]octane

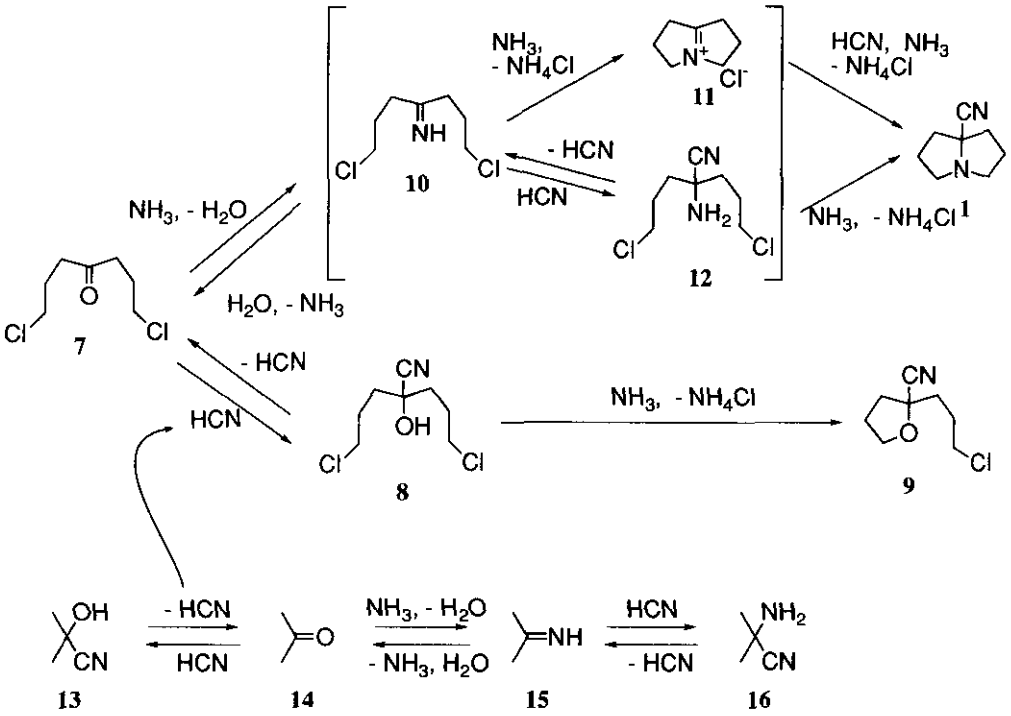
run	CN Source (eq)	N Source	Solvent	Time	Results (**1** : **8** : **9** : **7** / mole ratio(by ^{1}H-NMR))
1	KCN (1.0)	NH_3, NH_4Cl	H_2O-MeOH	24 h	14 : 22 : 42 : 22
2	AC. (10.0)	NH_3	no solvent	46 h	89 : 0 : 11 : 0
3	AC. (10.0)	NH_3	MeOH	47 h	84 : 0 : 16 : 0
4	AC. (10.0)	NH_3	benzene	48 h	no reaction
5	AC. (1.0)	NH_3	no solvent	141 h	64 : 0 : 0 : 36
6	AC. (3.0)	NH_3	no solvent	141 h	90 : 0 : 10 : 0
7	AMPN. (3.0)	NH_3	MeOH	24 h	**1** : y. 82 % *isolated*

AC. : acetone cyanohydrin, AMPN. : 2-amino-2-methylpropanenitrile



As a result, the reaction mechanism was postulated as follows. In the case when **7** reacted with ammonia, the imine intermediate (**10**) might be formed. Next, **10** might be ring-closed to give **11** or reacted with HCN to give **12**. Finally, **11** and **12** might be converted to **1**. On the other hand, **7** reacted with HCN to give **8**. Subsequently, it might be ring-closed to give **9**. In the reaction system, the equilibrium among **7**, **8**, **10** and **12** might be established. It is thought that the water, as the solvent, might shift the equilibrium between **7** and **10** to **7**, and

then the reaction from **7** to **8** might preferentially proceed to give **9**.



Scheme 3 The reaction mechanism of the formation of **1**

In order to shift the equilibrium to **10**, reactions in the organic solvent without water were examined. Acetone cyanohydrine (**13**) was used as the CN source because KCN had a low solubility in the organic solvents (MeOH or benzene) (runs 2, 3, and 4). As a result, the yield of **1** could be raised in the reaction with methanol and without the solvent. No reaction proceeded in benzene because of the low solubility of NH_3 in benzene. Furthermore, the other experiments were done with 1, 3, and 10 equivalents of acetone cyanohydrine versus **7** (runs 2, 5, and 6). Consequently, the higher the amount of acetone cyanohydrin, the faster the reaction proceeded and the less of **9** was formed.

In the reaction system using the organic solvents, we found evidence that **1** was formed after the translation of acetone cyanohydrine to **16**. The open circles in Figure 1 show the manner of the formation of **16** versus time. The closed circles mean the formation ratio of **1** / **9**. It was found that the ratio suddenly rose to a maximum in 60 hours. Therefore, we thought that if **16** was initially used as the CN source, the reaction time could be shortened, and furthermore, by-products could be reduced.

When **7** was reacted with **16** in no solvent, no by-product was formed and the reaction time was shortened. Also, the reaction in MeOH was completed after 24 hours, and gave **1** in 82% yield.[5]

The total reaction mechanism may be postulated as follows (Scheme 3).

When **13** was used as the CN source, the equilibrium among **13**, **14**, **15** and **16** might shift to **16** in the presence of excess NH_3. During the transformation of **13** to **16**, HCN might be formed, and HCN might react with **7** to give **8** and then **9**.When **16** was used as the CN source, the concentration of HCN in the system was low, and the equilibrium among **8**, **7** and **10** might shift to **10**, and **10** might turn into **11**. Next, **11** might react with HCN to give **1**.
We think that nucleophiles except for the CN group can be applied to this reaction, and 1-azabicyclo[m.n.0]alkane derivatives can be prepared by the modified reaction, which are now under investigation.

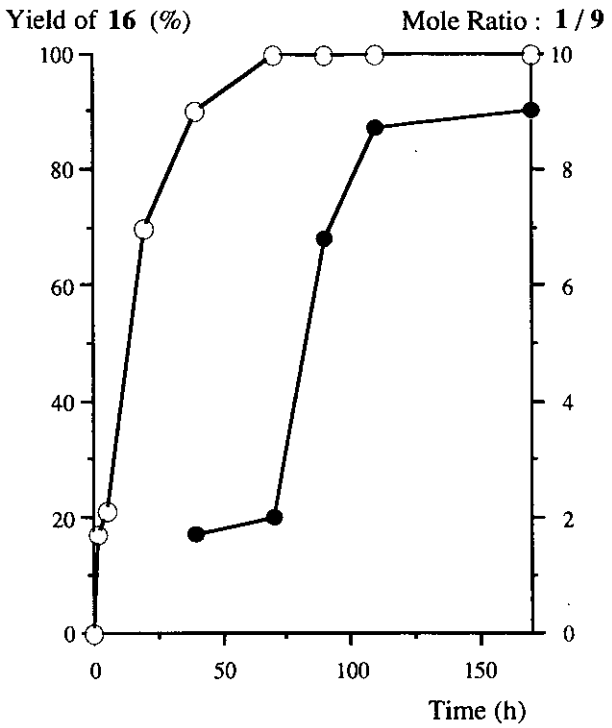


Figure 1 Yield of **16** (open circles) and mole ratio of **1/9** (closed circles) versus reaction time in the reaction of **7** with acetone cyanohydrine. These yields and mole ratios were monitored by ^{1}H-NMR.

REFERENCES AND NOTES

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4. Org.Syn., Coll. IV, 278, John Wiley & Sons, Inc., New York (1963).
5. Compound (**7**) (1.0 eq) reacted with **16** (3.0 eq) and NH_3 gas (10 eq) in MeOH (50 - 100 eq) at 20-25°C for 24 h. The reaction mixture was evaporated to remove excess NH_3 and solvent. And then, the residual oil was then distilled under reduced pressure to give **1** (Y. 82%).

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