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The reduction ring-opening reaction of imidazoline

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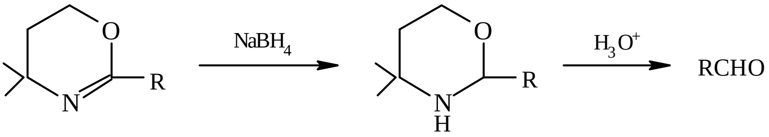
Abstract A new reduction ring-opening reaction of 2-imidazoline with sodium borohydride is reported, and the effect of reaction condition on the yield, reaction mechanism and the use of the new reaction in synthesis of ethylenediamine derivatives are discussed. A new method for the preparation of unsymmetrical substituted ethylenediamine via the reduction ring-opening reaction of imidazoline is provided.

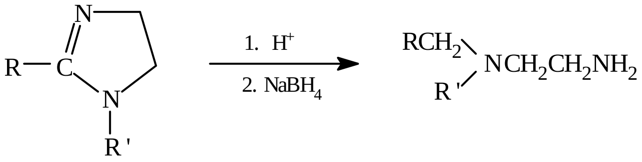
Keywords: imidazoline, reduction ring-opening reaction, ethylenediamine derivatives, synthetic method.

The reduction of six-membered heterocyclic compounds containing C═N double bond oxazine 1 with sodium borohydride was studied by Meyers et al.[1]. They found that the C═N double bond in the heterocyclic compounds was reduced to C—N single bond to form compound **2**, which hydrolyzed under acidic condition to give the corresponding aldehydes **3**. This provides a useful procedure for the preparation of aldehydes by the reduction-hydrolysis reaction of six-membered heterocyclic compounds with C═N double bond in the presence of sodium borohydride



1 **2** **3**

We have studied the reduction of five-membered heterocyclic compounds 2-imidazolines **4—10** with sodium borohydride. By treating 2-imidazolines with acid and reducing it by sodium borohydride, we obtained the ring-opening product N,N-disubstituted ethylenediamines **11—17**.



4—10 **11—17**

R' = H, R = n - $C_{11}H_{23}$ (**4**,**11**) n - $C_{15}H_{31}$ (**5**,**12**) n - $C_{17}H_{35}$ (**6**,**13**) C_6H_5 (**7**,**14**) CH_3 (**8**,**15**)

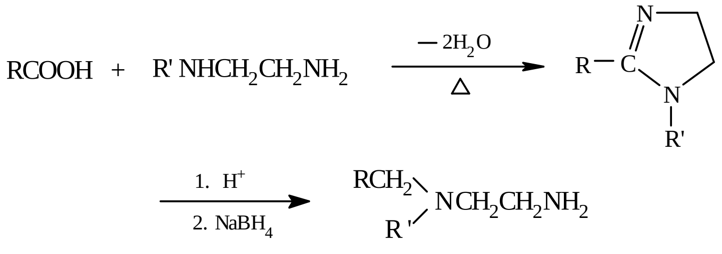
R' = $CH_2CH_2NH_2$, R = n - $C_{11}H_{23}$ (**9**,**16**)

R' = CH_2CH_2OH, R = n - $C_{11}H_{23}$ (**10**,**17**)

Compared with the reaction described by Meyers, the reaction of imidazoline with sodium borohydride achieves not only the reduction of C═N but ring-opening. The reaction reported by Meyers provides an important method for the preparation of aldehydes from heterocyclic compounds, the reduction ring-opening reaction reported in this paper provides a novel method to synthesize unsymmetrical substituted ethylenediamine from heterocyclic compounds.

In the reduction ring-opening reaction of 2-imidazoline, the polarized C═N double bond in 2-imidazoline is reduced by sodium borohydride and broken. We think that the reduction of C═N double bond is just like the reduction of C═O double bond with sodium borohydride. In this reaction, sodium borohydride donates hydride ion as a nucleophilic reagent, and hydride ion attacks the electron-deficient carbon atom in C═N double bond. When acid is added, the formation of nitrogenium ion improves the electrophilicity of carbon atom, making the reduction easy to happen. As 2-imidazolium is a five-membered ring, C═N double bond is apt to break to form ring-opening product when it is reduced to C-N single bond. If N-1,N-3 in 2-imidazoline are not substituted, the ring-opening reaction happens between N-1 and C-2 or between C-2 and N-3, and N-monoalkyl ethylenediamine is abtained. If N-1 is substituted, it becomes more difficult for the sodium borohydride to approach closely enough to the bond between N-1 and C-2. So the bond between C-2 and N-3 is broken, and N,N-dialkyl ethylenediamine is obtained. It is attributable to steric hindrance effect.

Imidazoline can be prepared from carboxylic acid and ethylenediamine or substituted ethylene-diamine, so the reduction ring-opening reaction of imidazoline provides a novel method for the preparation of unsymmetrical substituted ethylenediamine from carboxylic acid, ethylenediamine or substituted ethylenediamine via imidazoline.



In this synthetic method, carboxylic acid and alkyl ethylenediamine are used as starting materials, and alkyl group is attached to the secondary nitrogen atom in alkyl ethylenediamine via imidazoline intermediate. This method has not been reported in literature, but it is important in organic synthesis.

The ring-opening reaction of quaternary ammonium compounds, which were prepared from imidazol and alkyl halides, in the presence of sodium borohydride was reported by Godefrui et al.[2] The heterocyclic compounds and products described in literature are different from those discussed in this paper. Since ethylenediamine derivatives prepared by Godefrui's reaction have substituting group on both nitrogen atoms, this method cannot be used to synthesize monoalkyl ethylenediamines or ethylenediamine derivatives with two alkyl groups on one nitrogen. The special ring-opening reaction of five-membered imidazoline can be used in the synthesis of unsymmetrical ethylenediamines. So it is of more importance in orgaic synthesis than the reduction of C N double bond in six-membered heterocyclic compounds or other compounds with C═N double bond.

Here the effect of reaction condition on the yield of reduction ring-opening reaction is studied, and its uses in synthesis of ethylenediamine derivatives are discussed.

1 Experimental

1.1 Apparatus and reagents

Melting points were determined on a Model XT-2 melting point apparatus and uncorrected; IR spectra were recorded on a Perkin Elmer IR-440 spectrophotometer on a KBr matrix; NMR spectra were recorded in $CDCl_3$ solution with tetramethylsilane as internal standard on a Bruker AC-80 spectrometer; the products were separated by column chromatography on silica (200—300 mesh); all chemicals were of reagent grade.

1.2 Synthesis of 2-imidazolines (**4**—**10**)

2-Imidazolines (**4**—**10**) were prepared by procedures reported in literature[3—5]. The melting points and IR spectra of the compounds were consistent with those reported, and the absorption of C═N double bond in 2-imidazoline appeared as a characteristic absorption at about 1 600 cm^{-1}.

1.3 Synthesis of substituted ethylenediamines (**11**—**17**)

0.05 mol imidazoline intermediate and 80 mL isopropyl alcohol were mixed. The mixture was stirred, and the pH of the solution was adjusted to 7 by the addition of concentrated hydrochloric acid. Then a solution of 1.9 g (0.05 mol) sodium borohydride in 30 mL isopropyl alcohol was added dropwise. The mixture was stirred for 1 h. During the stirring, the pH of solution was maintained at 7 with concentrated hydrochloric acid. After 1 h the pH of mixture was adjusted to 2—3 with concentrated hydrochloric acid, and a lot of white solid appeared. After filtration, the solid was dissolved in a minimum amount of water, then the pH was adjusted to 9—10 with 40% sodium hydroxide. The mixture was heated slightly to make the precipitate dissolved, and extracted with chloroform (2×50 mL). The extracts were dried over anhydrous potassium carbonate, and after removal of chloroform by distillation, the residue was separated by column to give substituted ethylenediamines **11**—**17**.

The dihydrochlorides of compounds **11**—**13**: white crystals, m.p.: 222—224, 204—206, 194—196℃ respectively, all were in accord with those reported in ref. [6], yield 86.7, 85.9, 83.1%.IR: compound **11**, v_{max} :3300, 3200 (NH_2), 2950, 2900, 2850, 1640, 1605, 720 cm^{-1}; Compound **12**, v_{max}: 3300, 3200 (NH_2), 2960, 2910, 2850, 1640, 1600, 720 cm^{-1}; compound **13**, v_{max}: 3300, 3200 (NH_2), 2960, 2900, 2850, 1640, 1600, 720 cm^{-1}. Compounds **14** and **15** were converted to sulfonamides with p-bromobenzenesulfonyl chloride: white crystals, m.p.: 198—200, 126—128℃, in agreement with the data in ref.[7], yield 48.3, 40.1%. IR: compound **14**, ν_{max}: 3350, 3300 (NH_2), 3030, 2920, 2850, 1600, 1500, 750, 690 (C_6H_5)cm^{-1}; compound **15**, ν_{max}: 3380, 3300 (NH_2), 2960, 2920, 2840, 1604, 1450 cm^{-1}; Compound **16**: white sticky liquid, yield 72.5%, b.p.: 144℃ /266.6Pa, in accord with ref.[8], ν_{max}: 3350, 3300 (NH_2), 2950, 2920, 2860, 1630 (NH_2), 1465. compound **17**: light yellow sticky liquid, yield 72.4%, elementary analysis (%), found (calcd.): C 70.21 (70.46), H 13.18 (13.32), N 9.98 (10.27). IR: ν_{max}: 3400 (OH), 3350, 3300 (N-H), 1630 (N-H) cm^{-1}; ^{1}HNMR (δ ,$CDCl_3$): 0.87 (3H,t,CH_3), 1.26[20H,m,$(CH_2)_{10}$], 2.11(2H,t,NH_2), 2.78[6H, m, $N(-CH_2)_3$], 3.37-3.44(2H,m,CH_2N), 3.63-3.76(3H,m,CH_2OH).

2 Results and discussion

2. 1 Novel method for the preparation of N-alkyl ethylenediamine

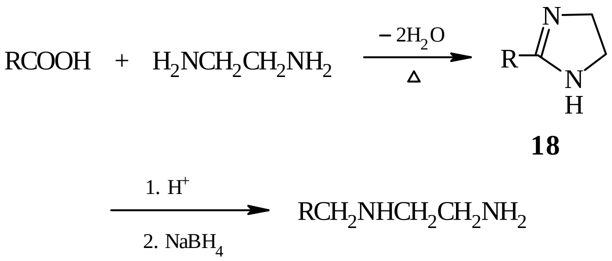
Direct alkylation of ethylenediamine gives a mixture of multi-substituted products. In literature, N-alkyl ethylenediamines were prepared via monoacetylation, benzenesulfonation, and alkylation of ethylenediamines, then acetyl group and benzenesulfonyl group were removed by hydrolysis under acidic condition [6].

$$H_2NCH_2CH_2NH_2 \xrightarrow{CH_3COOC_2H_5} H_2NCH_2CH_2NHCOCH_3$$

$$\xrightarrow[NaOH]{C_6H_5SO_2CI} C_6H_5SO_2NHCH_2CH_2NHCOCH_3 \xrightarrow[NaOH]{RX}$$

$$C_6H_5SO_2N(R)CH_2CH_2NHCOCH_3 \xrightarrow{HCI} RNHCH_2CH_2NH_2$$

In this paper, a novel synthetic method is provided for this kind of compounds by the reduction ring-opening reaction of imidazolines. The synthetic route is as follows:



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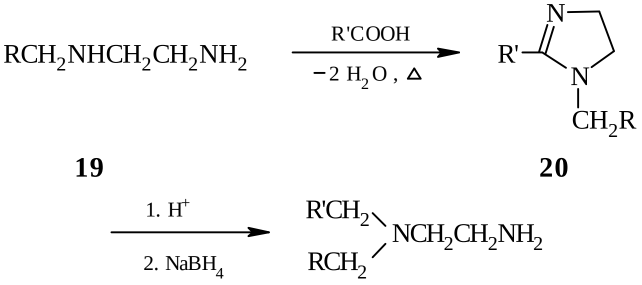
19

In this method, N-alkyl ethylenediamine **19** was prepared from carboxylic acid and ethylenediamine via cyclization, ring-opening reduction in the presence of sodium borohydride. Different from the synthetic methods in literature, this method employs carboxylic acids as starting materials. In other methods, the starting materials, alkyl halides, must be prepared from carboxylic acids or esters via alcohols, and besides, the protection of amino groups makes the reaction process complicated. The present method is easy, and the starting materials are readily available; it provides a simple procedure for the preparation of N-alkyl ethylenediamine, eapecially for long-chain N-alkyl ethyenediamine.

N-alkyl ethylenediamine **19** can react with carboxylic acids via cyclization to give 1,2-disubstituted 2-imidazoline **20**, and the reduction ring-opening reaction of compound **20** can give N, N-dialkyl ethylenediamine **21**



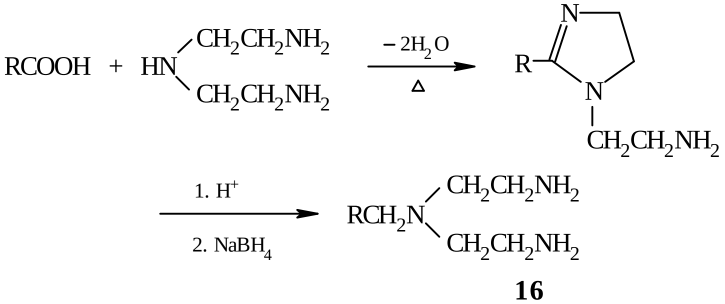
19 **20**

21

In N, N-dialkyl ethylenediamine **21**, there are two alkyl groups linking to the same nitrogen. It is difficult to prepare this compound via alkylation of ethylenediamine, because two alkyl groups, especially two different alkyl groups, must attach to one nitrogen atom. The reduction ring-opening reaction of 2-imidazoline provides a valuable method for synthesis of this kind of ethylenediamine derivatives; therefore this method can be used for the preparation of N, N-dialkyl ethylenediamines whether the two alkyls are the same or not by using different carboxylic acids.

2.2 Novel method for the preparation of 4-alkyl diethylenetriamine

The reduction ring-opening reaction of imidazoline is not only used in the synthesis of N-monoalkyl ethylenediamines, N, N-dialkyl ethylenediamines, but in the synthesis of 4-alkyl diethylenetriamines. For example, the synthetic route for 4-dodecyl diethylenetriamine **16** described in this paper is as follows:



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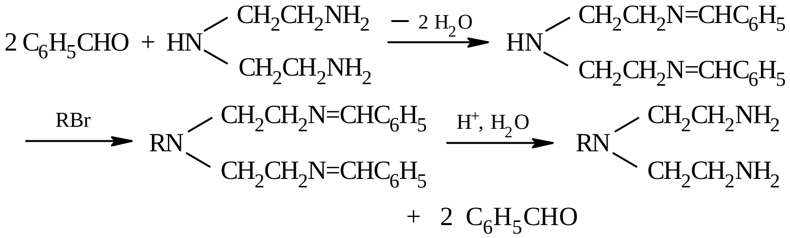
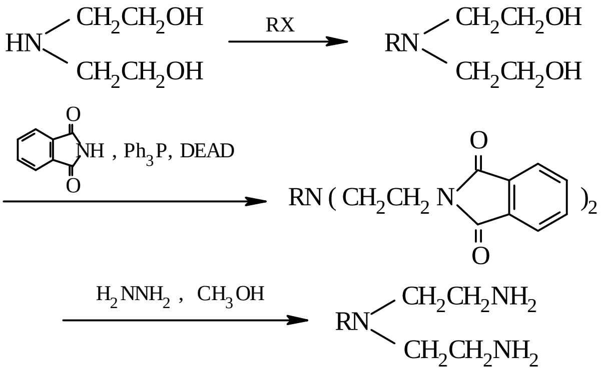
4-alkyl diethylenetriamines are widely used in medicine, daily chemical industry and waster handling, etc. The method described in ref.[9] for the preparation of 4-alkyl diethylenetriamines by protecting amino groups is as follows:



In this method, two primary amino groups in diethylenetriamine are protected by the C═N double bond which is formed via the reaction of diethylenetriamine and benzaldehyde. Then alkylating reaction happens in the fourth position of diethylenetriamine in the presence of alkyl halides, and 4-alkyl diethylenetriamine are obtained by hydrolysis under acidic condition.

Another method for the preparation of 4-alkyl diethylenetriamines was reported in ref. [10]. N-alkyl diethanolamines were obtained from diethanolamines and halides via alkylation, then using Gabrial’s method, two hydroxide groups at the end of the chain of N-substituted diethanolamines were replaced by amino groups, and 4-substituted diethylenetriamines were obtained.



In this method, special reagents including phthalimide, triphenyl phasphine, diethyl ammonium dithiocarbamate(DEAD), hydrazine are used. The method is complicated and the yields are poor.

4-alkyl diethylenetriamines can be prepared from diethylenetriamine and carboxylic acids via reduction ring-opening reaction of 2-imidazoline. Compared with the synthetic method described in literature, the starting material carboxylic acids are abundant, while the starting material alkyl halides used in literature method are prepared from the corresponding carboxylic acids or alcohols. This new method works easily and has good yield. The yield of the reaction to prepare imidazolines is about 90% and the reduction ring-opening reaction is about 70%—80%. If fatty acids are used as starting materials, long-chain hydrophobic alkyl group can be attached to the secondary nitrogen atom of diethylenetriamine. Three nitrogen atoms in long-chain alkyl diethlenetriamine can be attached with hydrophilic groups. So this new synthetic method can be used in the preparation of novel surfactants, especially surfactants with many functional groups.

2.3 Effect of reaction condition on yield

The reduction of 1-aminoethyl-2-undecyl-2-imidazoline to 4-dodecyl diethylenetriamine in the presence of sodium borohydride was studied to determine a suitable reaction condition. Three kinds of conditions were studied in the experiment: adding acid to make the solution acidic, neutral or not adding acid (imidazoline shows basic capacity itself). Poor yield was obtained in acidic condition for hydrolysis of sodium borohydride in the presence of acid. So we studied the reduction reaction mainly in neutral condition (adding acid) and basic condition(not adding acid).

It was found that the reaction of long-chain alkyl aminoethyl imidazoline was finished in higher yield under neutral condition rather than basic condition when the reaction temperature, reaction time, the ratio of mol value of imidazoline and sodium borohydride were the same. When the reaction solution was neutral, the reaction temperature 20℃, and the reaction time 1 h, the yield of reduction product was higher. Moderate excess of sodium borohydride could raise the yield because part of sodium borohydride was hydrolyzed by alcohol solvent or acid (adjusting pH 7). Higher yield was obtained when the ratio of imidazoline to sodium borohydride was 1:2.The solvent used in the reaction has influence on the yield of reaction. And it was found that isopropyl alcohol or the mixture of isopropyl alcohol and tetrahydrofuran were suitable solvents for the reaction.

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References

1. Politzer, I. R., Meyers, A. I., Aldehydes from 2-benzyl-4, 4, 6-trimethyl-5, 6-dihydro-1, 3(4H) oxazine, Org. Synth., 1971, 51: 24.
2. Godefrui, E. F., The reductive ring cleavage of 1,3-disubstituted imidazolium iodides by sodium borohydride, J. Org. Chem., 1968, 33(2): 860.
3. Mannheimer, H. S., Methods for producing imidazolines and derivatives thereof, USP 3 408 361, 1968, 10.
4. Shi Zhen, Li Na, The synthesis of alkylimidazoline dicarboxylate, Journal of Northwest University (Natural Science ed. in Chinese), 1994, 24(3): 219.
5. Hill, A. J., Aspinall, S. R., The preparation and cyclization of monoacylethylenediamines, J. Am. Chem. Soc., 1939, 61: 822.
6. Aspinall, S. R., Ethylenediamine, Ⅳ monoalkyl derivatives, J. Am. Chem. Soc., 1941, 63: 852.
7. Linsker, F., Evans, R. L., N-Alkylethylenediamines, J. Am. Chem. Soc., 1945, 67: 1581.
8. Eastman Kodak Company, Kodak Laboratory ＆ Research Products, New York:Eastman Kodak Company, 1987, 176.
9. Devinsky, F., Bittererova, F., Lacko, I., Amine oxides, Chem. Pap., 1985, 39(1): 125.
10. Riggio, G., Hopff, W. H., Hofmann, A. A., Specific ligands for the affinity chromatography of cholinergic proteins, Helv. Chim. Acta, 1980, 63(2): 488.