Preparation of Aliphatic Amines by the Leuckart Reaction

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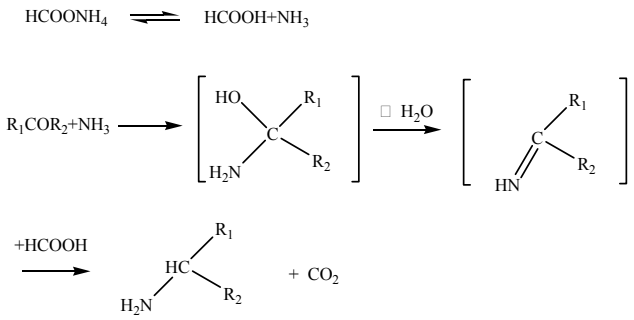
The in situ reductive amination of carbonyl compounds has been an important part of the synthetic chemist's repertoire since the introduction of a procedure based on the Leuckart reactions, conversion of certain ketones and aldehydes to the corresponding amines by heating with excess ammonium formate[1,2]. While this reaction has been very extensively investigated in aromatic compounds very little work has been done with aliphatic compounds other than terpenoid ketones. Wallach, representative of many predecessors proposed the mechanism of the reaction were as follows[3,4]:



And they thought the impossible intermediate for this reaction in the form of the aliphatic imine ($R_1R_2C=NH$), which only one double bond was present. The proposed intermediate, however, contains a conjugate system of two double bonds at least[5].

We have been studying this reaction as a possible preparative procedure for wholly aliphatic amines and have obtained some rather interesting results. The Leuckart reaction gives generally good yields of products, furthermore, we do propose to offer some novel mechanisms in this report.

1.Experimental

1.1 Apparatus and reagents

A Milestone ATC-300 microwave laboratory system was used to perform the microwave reaction. ^{1}H NMR spectra were measured on the Bruker ARX-300 and ARX-400 spectrometer using $CDCl_3$ as solvent. Mass chromatographic analysis were performed using a Agilent-1100 series LC/MS Trap mass analyser. All the regents used were analytical grade without further purification.

1.2 Procedure

The following procedures are typical example of the experiments reported in the following Table 1. This reaction may be used to prepare the corresponding primary amines in satisfactory yields from a large number of aliphatic ketones with only a slight modification of the experimental conditions.

2-Heptylamine (i). To a 250ml four-necked flask, equipped with a dropping-funnel, thermometer, water segregator and down-directed condenser, was added with care 54g (0.86 mol) of ammonium formate. The temperature was raised to 120℃ by melting the solid with stirring, and 19.8 g (0.172 mol, 99%) of 2-oenanthone was added when the ammonium formate melted completely. The temperature was maintained at 130-140° for seven hours and any ketone which distilled was returned to the flask at intervals. The formyl derivative was hydrolyzed in the reaction mixture by refluxing for eight hours with 110℃ of concentrated hydrochloric acid (36-38%). After standing overnight, the mixture was diluted with 100 ml of water and filtered the foreign matter. The Filtrate extracted with 50ml ether to remove water-insoluble material. Aqueous solution was made alkaline with 15% NaOH solution and the oil thus produced extracted with 150ml ether. The ether solution was put together and washed three times with 100 ml NaH_2PO_3 buffer (pH 3.3-3.4) , so most of 2-heptylamine was solved in the buffer solution. Adjusted alkalinity (pH 9-10) with 15% NaOH solution again and extracted with ether three times (80ml, 50ml, 30ml) dried with anhydrous calcium chloride and the ether removed by distillation under reduced pressure. The residue gave 11 g (56%) of 2-heptylamine (purity: 99%). ^{1}H NMR ($CDCl_3$, δ ppm): 2.86 (t, 1H, J=11.6Hz, CH), 2.17(d, 2H, J=6.4Hz, NH_2), 1.25~1.31(m, 8H, CH_2), 1.04~1.07(m, 3H, CH_3), 0.84~0.87(m, 3H, CH_3). MS (ESI-MS): 116.1 $[M+H]^+$.

(2) Propylamine (a)

^{1}H NMR ($CDCl_3$, δ ppm): 2.65~2.76 (m, 2H, CH_2), 1.45~1.53 (m, 2H, CH_2), 1.24(s, 2H, NH_2), 0.92 (t, 3H, J=6.8Hz, CH_3). MS (ESI-MS): 60.1 $[M+H]^+$.

(3) Isopropylamine (b)

^{1}H NMR ($CDCl_3$, δ ppm): 2.92~3.00 (m, 1H, CH), 1.17 (t, 2H, J=3.6Hz, NH_2), 0.91 (d, 6H, J=6.4Hz, CH_3). MS (ESI-MS): 60.3 $[M+H]^+$.

(4) Butylamine (c)

^{1}H NMR ($CDCl_3$, δ ppm): 2.68~2.75 (m, 2H, CH_2), 1.77 (s, 2H, NH_2), 1.33~1.66 (m, 4H, CH_2), 0.92 (t, 3H, J=6.4Hz, CH_3). MS (ESI-MS): 74.6 $[M+H]^+$.

(5) 2-Butylamine (d)

^{1}H NMR ($CDCl_3$, δ ppm): 2.79~2.95 (m, 1H, CH), 1.36~1.50 (m, 2H, CH_2), 1.25 (t, 2H, J=4.0Hz, NH_2), 1.05 (d, 3H, J=5.6Hz, CH_3), 0.92 (t, 3H, J=7.2Hz, CH_3). MS (ESI-MS): 74.3 $[M+H]^+$.

(6) Pentylamine (e)

^{1}H NMR ($CDCl_3$, δ ppm): 2.68~2.77 (m, 2H, CH_2), 1.02~1.58 (m, 6H, CH_2), 1.12 (s, 2H, NH_2), 0.91 (t, 3H, J=6.4Hz, CH_3). MS (ESI-MS): 88.2 $[M+H]^+$.

(7) 1-Methylbutylamine (f)

^{1}H NMR ($CDCl_3$, δ ppm): 2.88~3.12 (m, 1H, CH), 1.24~1.36 (m, 4H, CH_2), 1.26 (d, 2H, J=3.6Hz, NH_2), 1.01 (d, 3H, J=6.0Hz, CH_3), 0.88~0.93 (m, 3H, CH_3). MS (ESI-MS): 88.1 $[M+H]^+$.

(8) 1-Ethylpropylamine (g)

^{1}H NMR ($CDCl_3$, δ ppm): 2.55~2.64 (m, 1H, CH), 1.70 (d, 2H, J=5.2Hz, NH_2), 1.46 (m, 2H, CH_2), 1.28 (m, 2H, CH_2), 0.91 (t, 3H, J=8.0Hz, CH_3). MS (ESI-MS): 88.2 $[M+H]^+$.

(9) Cyclopentylamine (h)

^{1}H NMR ($CDCl_3$, δ ppm): 3.31~3.43 (m, 1H, CH), 1.82~1.93 (m, 2H, CH_2), 1.72~1.76 (m, 2H, CH_2), 1.55 (t, 2H, J=5.6Hz, CH_2), 1.37 (d, 2H, J=5.6Hz, NH_2), 1.28~1.32 (m, 2H, CH_2). MS (ESI-MS): 86.1 $[M+H]^+$.

(10) Hexylamine (i)

^{1}H NMR ($CDCl_3$, δ ppm): 2.68~2.88 (m, 2H, CH_2), 1.44~1.63 (m, 2H, CH_2), 1.08~1.41 (m, 6H, CH_2), 1.17 (s, 2H, NH_2), 0.90 (t, 3H, J=6.8Hz, CH_3). MS (ESI-MS): 102.1 $[M+H]^+$.

(11) Cyclohexylamine (j)

^{1}H NMR ($CDCl_3$, δ ppm): 2.62~2.78 (m, 1H, CH), 1.44~1.97 (m, 5H, CH_2), 0.72~1.44 (m, 5H, CH_2), 1.18 (s, 2H, NH_2). MS (ESI-MS): 100.6 $[M+H]^+$.

(12) Heptylamine (k)

^{1}H NMR ($CDCl_3$, δ ppm): 2.63~2.77 (m, 2H, CH_2), 1.41~1.53 (m, 2H, CH_2), 1.40 (t,

2H, J=3.2Hz, NH_2), 1.18~1.39 (m, 8H, CH_2), 0.89 (t, 3H, J=6.8Hz, CH_3). MS (ESI-MS): 116.3 $[M+H]^+$.

(13) Octylamine (m)

^1H NMR ($CDCl_3$, δ ppm): 2.68~2.79 (m, 2H, CH_2), 1.69 (s, 2H, NH_2), 1.28~1.43 (m, 12H, CH_2), 0.89 (t, 3H, J=5.2Hz, CH_3). MS (ESI-MS): 130.7 $[M+H]^+$.

(14) 2-Octylamine (n)

^1H NMR ($CDCl_3$, δ ppm): 2.84 (t, 1H, J=9.6Hz, CH), 1.55 (s, 2H, NH_2), 1.29~1.40 (m, 10H, CH_2), 1.05~1.09 (m, 3H, CH_3), 0.89~0.91 (m, 3H, CH_3). MS (ESI-MS): 130.3 $[M+H]^+$.

concentrated hydrochloric acid (36-38%) as the reducing agent refluxing for eight hours.

2. Results and Discussion

2.1 Effect of different reagents

We found that some water was generated in the water segregator within ammonium formate melting. According to Wallach's view there were not water except for formic acid and ammonia. We suggested formamide was generated by deaquation of ammonium formate, and the reaction system was quite complex including formamide, water, ammonium formate, formic acid and ammonia (the last two were generated by hydrolysis). In order to study each reagent how to effect the the yield of amine, a series of experiments were ran with 2-oenanthone. The reactions were carried out in the reaction to undergo the same steps as above.

entry	reagent	temp(℃)	time (h)	yield (%)
1	formamide	170-180	21	15
2	formamide and water	170-180	21	16
3	ammonium formate	120-130	7	56
4	ammonium formate*	120-130	7	27
5	formamide and ammonium formate	170-180	12	51
6	formamide and ammonium formate *	170-180	12	58
7	formic acid and ammonia	120-130	8	55
8	formamide and formic acid	170-180	20	63

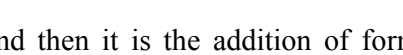
*: removed the water segregator and kept water in reaction system.

Formamide gives a lower yield of product whether the water is removed. When water is removed, a mixture of formamide and formic acid gives the best yields; ammonium formate gives better yields than formamide; a mixture of formamide and ammonium formate is as good as ammonium formate alone but no better. However, when no water is removed, the mixture is better than ammonium formate alone. It will be observed that in every case formamide is initially present or can easily be formed by dehydration of ammonium formate, a reducing agent is required. The examination of Table 2 shows that all of the compositions played respective role in the reaction.

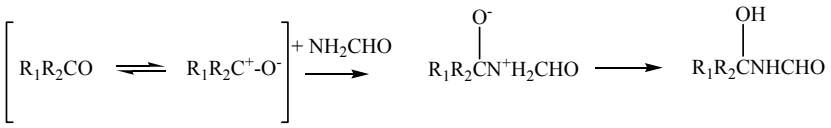
2.2 Possible mechanism

Now that formamide, water, ammonium formate and formic acid are active in this reaction and influenced each other, we must consider all of the facts. A possible general mechanism system is proposed and these reactions were taking place simultaneously.

At first ammonium formate easily dehydrated to formamide under heating



And then it is the addition of formamide to the carbonyl carbon, present as the familiar resonance form [$R_1R_2C^+$-O^-].



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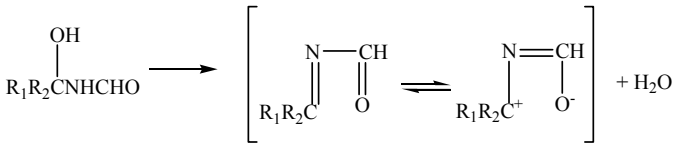
When water is split out, a stabile conjugate system is formed.



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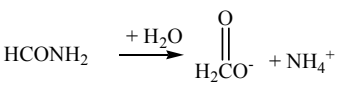
Little water still in the vessel under 120-130℃, therefore it can hydrolyze some formamide to give a small concentration of ammonium formate, including some undecomposed ammonium formate, which can serve as the reducing agent which the reaction requires.



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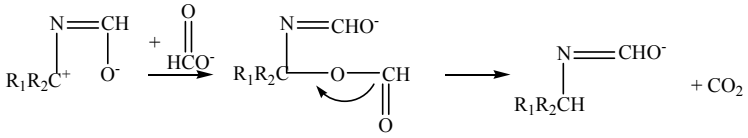
In a solution containing formamide (which has a very high dielectric constant) ammonium formate is probably highly ionized. The most reasonable mechanism for the reduction by ammonium formate consists of the addition of the formate ion to the positive center of the formimido compound, followed by **a** hydride ion shift with the subsequent release of carbon dioxide.



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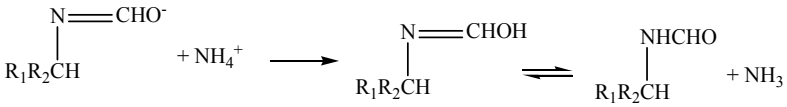
The ammonium ion gives up a proton to the intermediate and forms the aliphatic amide.



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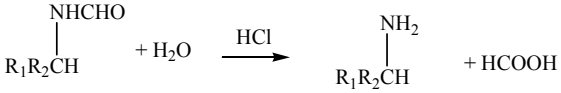
At last the aliphatic amide is hydrolyzed to aliphatic amine.



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Water is a very important factor fellow Table 1 and the mechanism. The removal of water facilitates the formation of formamide from the ammonium formate as well as the formation of the intermediate of step 2**.** But it is unwise to remove water completely because formamide can't hydrolyze in step 3.

3 conclusion

A good method of obtaining aliphatic amines, based on the Leuckart synthesis, is described. It has been applied to the preparation of several old and new aliphatic amines. Comparative datas on various reagents have been tabulated and a systemic mechanism is advanced for the synthesis of aliphatic amines.

Reference

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