CHEMISTRY LETTERS, pp. 1057-1060, 1978. Published by the Chemical Society of Japan

# A NOVEL METHOD FOR THE PREPARATION OF PRIMARY AMINES BY THE USE OF N-BENZYLHYDROXYLAMINE AND 2-FLUOROPYRIDINIUM SALT

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Primary amines were prepared from alkyl halides or olefinic compounds by the use of N-benzylhydroxylamine and 2-fluoro-1-methylpyridinium p-toluenesulfonate.

Primary amines are synthesized by the direct alkylation of ammonia with alkyl halides, but a major drawback consists of polyalkylation. The solution to the problem then lies in the prior replacement of extra hydrogens on nitrogen with other groups. As represented by the Gabriel synthesis,[1)] acyl groups are often used for the protection of N-H groups. Further, the use of N-substituted bis (arylsulfenyl) amine provided a convenient method especially for the preparation of amino compounds having nitrile, ester, amide, and carbonyl groups in the same molecule.[2)]

In the present experiment, a new method for the preparation of primary amines was studied based on the consideration that N-alkylhydroxylamine having two functionalities (an amino group and a hydroxyl group) would be a useful synthetic intermediate. Primary amines would be prepared by the following sereies of reactions; a) the N-alkylation of N-benzylhydroxylamine **1**[3)] by alkyl halide, b) the dehydration of the corresponding N-alkyl-N-benzylhydroxylamine **2** yielding N-benzylidenealkylamine **3**, c) acid hydrolysis of **3**.

At first, the N-alkylation of N-benzylhydroxylamine was investigated. Generally, the alkylation of hydroxylamine and its derivatives is carried out in protic solvents (ethanol, water, etc.) under refluxing conditions.[4)] On the other hand, we now found that hexamethylphosphoric triamide (HMPA) is the best solvent for the N-alkylation of N-benzylhydroxylamine, and the reaction of N-benzylhydroxylamine with phenethyl bromide in HMPA afforded the corresponding N-alkylated product in good yield at room temperature. The results of the solvent effect for the alkylation of N-benzylhydroxylamine by phenethyl bromide are summarized in Table I.

Table I. The Preparation of N-Benzyl-N-phenethylhydroxylamine[a)]

| Solvent | Yield[c)] |
|---|---|
| $C_6H_6$ | 0% |
| THF | 0% |
| DMF | 30% |
| HMPA | 83% |
| HMPA[b)] | 87% |
| EtOH | 71% |

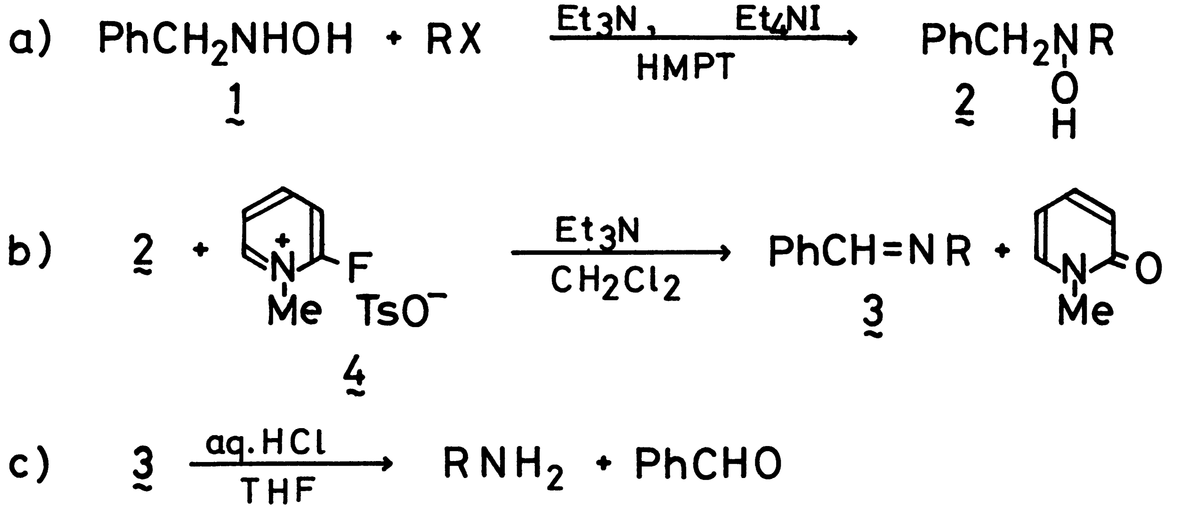
a) The reaction was carried out at room temperature for 24 h in the presence of an equimolecular amount of triethylamine.

b) An equimolecular amount of tetraethylammonium iodide was added.

c) Isolated yield.

N-Alkyl-N-benzylhydroxylamine thus formed was easily dehydrated by the use of 2-fluoro-1-methylpyridinium p-toluenesulfonate 4 and triethylamine in good yield[5)] and the hydrolysis of the corresponding N-benzylidenealkylamine 3 in dilute hydrochloric acid gave a primary amine.

A novel method for the preparation of primary amines was thus established using the above mentioned three reactions (eq. a), b), c)).



A typical procedure is described for the preparation of n-octylamine: to a mixture of 1 (2.28 mmol) and tetraethylammonium iodide (1.04 mmol) in HMPA (2 ml) was added a mixture of n-octyl bromide (2.08 mmol) and triethylamine (2.50 mmol) in HMPA (2 ml) under an argon atmosphere and the mixture was stirred for 40 h at room temperature. Water was then added and the aqueous solution was extracted three times with ether. The ether extract was washed twice with water and dried over anhydrous magnesium sulfate and evaporated to give a colorless oil. To a suspension of the above oil and 4 (2.49 mmol) in dichloromethane (3 ml) was added triethylamine (4.98 mmol) in dichloromethane (3 ml) at 0°C and the reaction mixture was stirred for 3 h at an ambient temperature. Saturated aqueous solution of sodium carbonate (10 ml) was then added and an organic layer was extracted three times with ether and washed with water. The ether layer was evaporated in vacuo and the residue was taken in 2 N hydrochloric acid (10 ml) and tetrahydrofuran (5 ml).

The reaction mixture was refluxed for 3 h, cooled and extracted twice with ether. The aqueous layer was neutralized with 2 N sodium hydroxide and extracted four times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo leaving almost pure n-octylamine, which was distilled to give n-octylamine (bp. 105-110°C/85 mmHg) in 75% yield.

In a similar manner, various primary amines were prepared in yields as summarized in the following Table II.

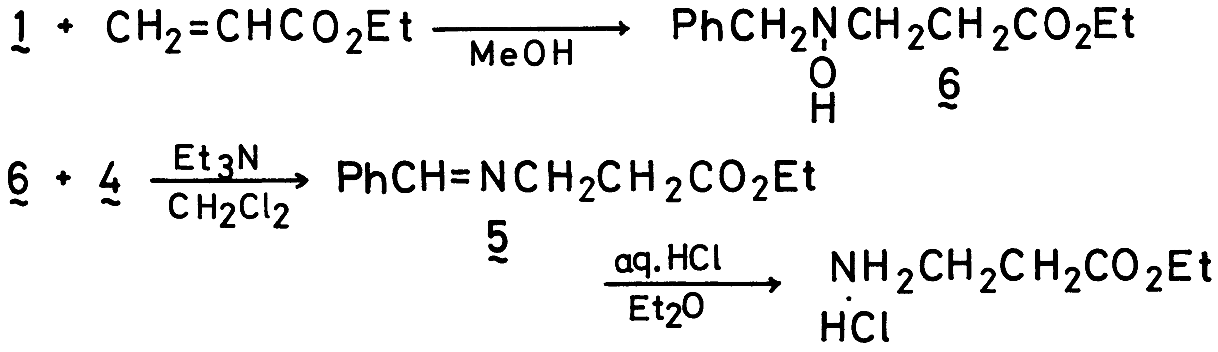
Table II. The Preparation of Primary Amines

| RX[a)] | Yield[b)] |
|---|---|
| $CH_3(CH_2)_7Br$ | 75% |
| $CH_3(CH_2)_{11}Br$ | 69% |
| $C_6H_5CH_2Br$ | 83% |
| $C_6H_5CH_2CH_2Br$ | 67% |
| $C_6H_5OCH_2CH_2Br$ | 63% |

a) N-Benzylhydroxylamine was not alkylated by secondary alkyl bromide (cyclohexyl bromide).

b) Primary amines were isolated by distillation and identified by comparison of NMR and IR spectra with those of authentic samples.

N-Alkyl-N-benzylhydroxylamine was also prepared by the Michael addition of N-benzylhydroxylamine to olefinic compounds[6)] as follows; a solution of N-benzylhydroxylamine **1** (3 mmol) and ethyl acrylate (3 mmol) in methanol (3 ml) was stirred overnight at room temperature. Then methanol was evaporated in vacuo to give a colorless oily residue. To a mixture of the residue and 2-fluoro-1-methylpyridinium p-toluenesulfonate **4** (3.6 mmol) in dichloromethane (2 ml) was added triethylamine (7.2 mmol) in dichloromethane (2 ml) under an argon atmosphere. The reaction mixture was stirred for 3 h at room temperature. Water was then added and the organic layer was extracted three times with ether and washed with water. The ether extract was dried over anhydrous magnesium sulfate and evaporated in vacuo. The oily residue was distilled to give ethyl N-benzylidene-3-aminopropionate **5** (bp. 130°C/1.7 mmHg, found: C, 70.08; H, 7.20; N, 6.78%. calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%) in 82% yield.[7)] The benzylidene derivative **5** (1 mmol) was taken in 0.2 N hydrochloric acid (10 ml) and ether (5 ml) at 0°C and stirred for 7 h. The reaction mixture was extracted with ether and the aqueous layer was evaporated in vacuo at room temperature to give ethyl 3-aminopropionate hydrochloride in quantitative yield (mp. 65-67°C).



$$\mathbf{1} + CH_2{=}CHCO_2Et \xrightarrow[MeOH]{} PhCH_2\underset{OH}{N}CH_2CH_2CO_2Et\ \ \mathbf{6}$$

$$\mathbf{6} + \mathbf{4} \xrightarrow[CH_2Cl_2]{Et_3N} PhCH{=}NCH_2CH_2CO_2Et\ \ \mathbf{5} \xrightarrow[Et_2O]{aq.HCl} NH_2CH_2CH_2CO_2Et\cdot HCl$$

## References and Notes

1) a) S. Gabriel, Ber., 20, 2224 (1887).
b) M. S. Gibson and R. W. Bradshaw, Angew. Chem., 80, 986 (1968).

2) T. Mukaiyama, T. Taguchi, and M. Nishi, Bull. Chem. Soc. Jpn., 44, 2797 (1971).

3) N-Benzylhydroxylamine was prepared according to the following literature, see L. W. Jones and C. N. Sneed, J. Am. Chem. Soc., 39, 674 (1917).

4) S. R. Sandler and W. Karo, "Organic Functional Group Preparations" Vol. 3, Academic Press New York and London (1972), p. 321.

5) In order to compare the synthetic utility of the present onium salt **4** with commonly known dehydrating reagents, the similar dehydration of N-alkyl-N-benzylhydroxylamine was tried using p-toluenesulfonyl chloride. But the reaction was very slow and gave a complex mixture. Concerning the use of acyl halide, such as benzoyl chloride, it was reported8) that the reaction was very sluggish and the yield of imine was not so good.

6) A. A. R. Sayigh, H. Ulrich, and M. Green, J. Org. Chem., 29, 2042 (1964).

7) Similarly ethyl N-benzylidene-3-aminobutyrate and N-benzylidene-3-aminobutyronitrile were obtained in 70% and 54% yields from ethyl crotonate and crotononitrile.

8) S. Oae and T. Sakurai, Bull Chem. Soc. Jpn., 49, 730 (1976).

(Received July 10, 1978)