The Formic Acid–Formaldehyde Methylation of Amines[1]

STANLEY H. PINE* AND BERNARD L. SANCHEZ

Department of Chemistry, California State College, Los Angeles, California 90032

Received August 26, 1970

The formic acid–formaldehyde methylation of benzylamines has been investigated relative to reaction parameters and competing reactions. The formation of tertiary amine is favored over secondary amine, even when less than stoichiometric amounts of formaldehyde are used. Excess formaldehyde gives only a small increase in the tertiary amine yield. Formation of benzaldehyde is markedly reduced by the addition of sodium formate, presumably through enhancement of the reduction step of the methylation sequence. The absence of acid or specific base catalysis of the aldehyde formation along with a substituent effect trend suggests that the carbonyl side product results from hydrolysis of a benzylideneamine formed in an oxidation–reduction sequence of primary amine and Schiff base.

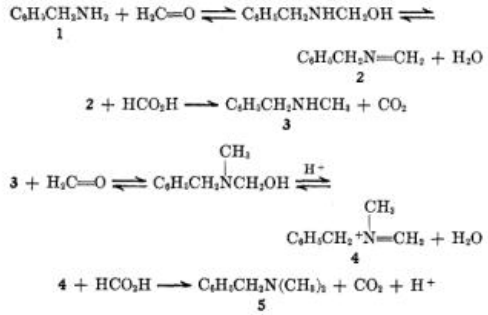
Although the formic acid–formaldehyde (Eschweiler–Clarke[2,3]) methylation of amines is a method of extensive synthetic utility,[4] it has received only limited critical investigation.[4a,5] In contrast to the mixtures which are often obtained through the methylation of primary amines with methyl iodide, the formic acid–formaldehyde method generally leads to good yields of the *N,N*-dimethyl tertiary amines. In some cases the formation of a carbonyl product derived from the amine can markedly reduce the useful yield.[6]

In the following, we have used benzylamines as our model and have approached the reaction from three aspects: (1) in what way do the reaction parameters affect the synthetic utility of the reaction, (2) what is the origin of the carbonyl side product, and (3) can the reaction mechanism be more clearly defined through the use of proposed intermediates and the detection of minor side products?

Results and Discussion

The formation of *N,N*-dimethylbenzylamine (**5**) from benzylamine (**1**) using formic acid–formaldehyde is expected to follow the sequence given in Scheme I. Work

SCHEME I



using ^{14}C-labeled formaldehyde or formic acid has confirmed that under the usual reaction conditions the methylation can be attributed to the formaldehyde and the reduction to the formic acid.[7]

When benzylamine (**1**) in 3 molar equiv of formic acid (88%) is allowed to react with 0.5–4.0 molar equiv of formaldehyde at 80°, the major basic product is *N,N*-dimethylbenzylamine (**5**) accompanied by small amounts of unreacted starting material **1** and *N*-methylbenzylamine (**3**). In addition, benzaldehyde (**6**), *N*-benzylformamide (**7**), *N*-benzyl-*N*-methylformamide (**8**), and *N*-methyldibenzylamine (**9**) are found. Selected reactions run at 50° provide comparable results with a considerably decreased rate of reaction.

As is illustrated in Figure 1, the yield of tertiary amine **5** increases in a nearly linear manner with increasing formaldehyde up to 1.5 molar equiv and then appears to level off somewhat below the maximum theoretical yield. Consistent with this is the corresponding decrease in primary and secondary amines, **1** and **3**, respectively, found principally as the formamides in the reaction mixture. These results demonstrate that formation of the tertiary amine **5** is the preferred reaction pathway, even when less than a stoichiometric amount of formaldehyde is utilized. The secondary to tertiary amine methylation is clearly faster than the primary to secondary amine reaction.

Formamide formation slows the methylation sequence by making the amine less available. A similar result has been observed in the related Wallach reaction.[8] When *N*-benzylformamide (**7**) is used as the starting material in an excess of formaldehyde, only about 50% of the amide is hydrolyzed and converted to further products. In this case the major reaction product is the Schiff base **2**, since insufficient formic acid is produced by the hydrolysis of **7** for complete reduction. Tertiary amine **5** and a trace of secondary amide **8** account for the formic acid released.

In order to demonstrate the importance of the Schiff base **2** in the proposed reaction scheme, a run using preformed **2** was carried out under the usual reaction conditions. As shown in Table I, the results are very similar to a run starting with benzylamine (**1**).

The formation of a carbonyl product, in this case benzaldehyde (**6**), generally is observed in the formic acid–formaldehyde methylation reaction and can reduce the synthetic utility.[6] The formation of such a carbonyl product has generally been attributed to hydrol-

(1) Acknowledgment is made to the National Science Foundation, to the donors of the Petroleum Research Fund administered by the American Chemical Society, and to the California State College, Los Angeles Foundation, for partial support of this work.

(2) W. Eschweiler, *Chem. Ber.*, **38**, 880 (1905).

(3) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

(4) (a) M. L. Moore, *Org. React.*, **5**, 301 (1949); (b) L. Spialter and J. A. Pappalardo, "The Acyclic Aliphatic Tertiary Amines," Memillan, New York, N. Y., 1965, p 45.

(5) A. F. Meiners, C. Bolze, A. L. Scherer, and F. V. Morriss, *J. Org. Chem.*, **23**, 1122 (1958).

(6) W. E. Parham, W. T. Hunter, R. Hanson, and T. Lahr, *J. Amer. Chem. Soc.*, **74**, 5646 (1952).

(7) W. Tarpey, H. Hauptmann, B. M. Tolbert, and H. Rapoport, *ibid.*, **72**, 5126 (1950).

(8) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).