# The Vilsmeier-Haack Formylation of 1,2,3-Trimethylindole



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The title reaction yields mainly a side-chain monosubstituted formyl derivative, namely 2-(1,3-dimethylindolyl)acetaldehyde.

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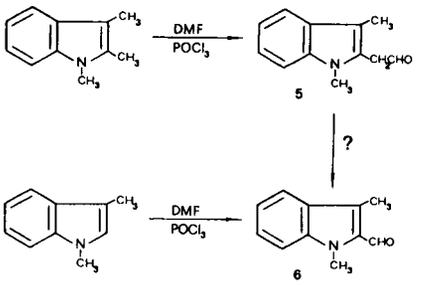
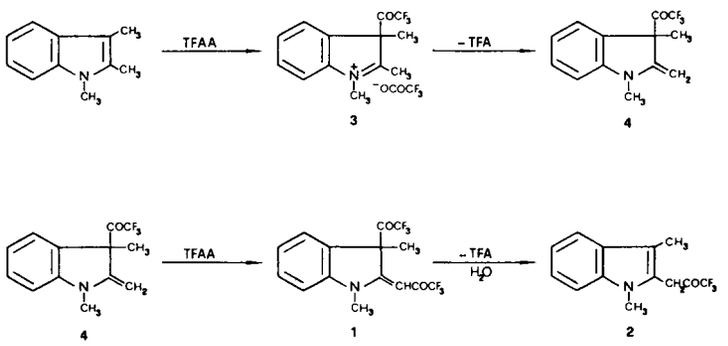
In the course of the continous interest of our group in the quantitative aspects of electrophilic substitutions of heteroaromatic compounds, we had published previously the relative rates of the Vilsmeier-Haack formylation of indole and a number of alkylindoles (1). In particular the main reaction product obtained from 1,2,3-trimethylindole was believed to be substituted at the homocyclic ring, by analogy with the substitution at the 6-position observed in the acetylation reaction (2) and the similar result obtained in the Vilsmeier-Haack formylation of *N*-methyl-1,2,3,4-tetrahydrocarbazole (3).

However, our subsequent work on the occurrence of non-conventional substitution pathways in halogenation (4) and acetylation (5) of 2,3-dimethylbenzofuran, as well as the known importance of *ipso*-attack to C-3 in alkylation (6) and acylation (7) of 3-substituted indoles, cast some doubt on this attribution. Moreover, a recent report (8) and our systematic study (9,10) on the trifluoroacetylation by trifluoroacetic anhydride (TFAA) in 1,2-dichloroethane, carbon tetrachloride or benzene, of several alkylindoles and, in particular, 1,2,3-trimethylindole showed that the main product of this reaction is the disubstituted compound **1**, which easily loses a molecule of trifluoroacetic acid during the usual work-up of the organic layer, to yield the monosubstituted side-chain product **2**. Spectral evidences on the mechanism were presented therein (10) suggesting that the reaction proceeds *via* a preliminary attack at C-3 to form a stable indoleninium ion pair (**3**), which slowly loses trifluoroacetic acid (TFA) from the trifluoroacetate anion and one of the slightly acidic protons of the 2-methyl group, yielding a 2-methyleneindoline (**4**). This in turn can undergo further substitution at the enaminic residual giving **1**, which leads to **2** on intervention of water (Scheme). The intramolecular rearrangement of the trifluoroacetyl group linked at C-3 to the 2-$CH_2$ position, typical of non conventional substitution, could be excluded (9,10) thus indicating that this reaction is much slower, in the organic medium, than the second attack by the electrophile.

In view of the close similarities between the mechanism of the trifluoroacetylation (11) and the Vilsmeier-Haack formylation (12) reactions, we have reinvestigated the latter reaction in order to verify whether the mechanism just described could apply generally for electrophilic substitutions of 1,2,3-trimethylindole, or the direct attack at the homocyclic ring could compete depending upon the steric requirements of the actual electrophile.




1,2,3-Trimethylindole (1 g) in *N,N*-dimethylformamide (1 ml) was added dropwise under stirring at room temperature to a mixture of phosphorus oxychloride (2.4 ml) and *N,N*-dimethylformamide (1 ml) and allowed to

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stand for 15 minutes in order to ensure the formation of the formylating complex. The molar ratio substrate: DMF:phosphorus oxychloride was therefore 1:2:2. The mixture was kept at room temperature for about two hours, then iced water (25 ml) was added, the organic layer washed with sodium bicarbonate dried over sodium sulfate and the solvent evaporated. The gas chromatographic analysis showed, besides some unreacted material (5-10%), the presence, in over 80% yield, of a single main product with a molecular weight of 187 (m/e$^+$, gc-ms), corresponding to a monoformyl derivative **5**.

The reaction was repeated several times under slightly different conditions. The same result was obtained when the mixture was heated to 75° for up to one hour. When the heating was prolonged, the relative amount of phosphorus oxychloride was increased, or the temperature went out of control during the work-up, significant amounts (up to 10%) of unidentified side products were observed, whose mass spectra indicated the presence of indole derivatives, (i) containing two methyl groups, m/e 173, and (ii) containing two methyl groups and two formyl groups, m/e 201.

Attempts at isolating the product by column chromatography or preparative gas chromatography for structure identification failed because of its great tendency to give black polymers. However, it was possible to isolate the pure compound from the crude product by simply washing the oil residue with diethyl ether: a white low melting solid remained insoluble and could be filtered off (yield *ca.* 50%). Its nmr spectrum in carbon tetrachloride exhibited the following signals: $\delta$ 2.17 (3H, s, 3-Me), $\delta$ 3.45 (3H, s, N-Me), $\delta$ 3.68 (2H, d, 2-$CH_2$), $\delta$ 6.80-7.50 (4H, m, Ar-H), $\delta$ 9.45 (1H, t, CHO). The absence of a third methyl group and the coupling between the aldehyde proton and the methylene protons positively indicate that the formyl group has substituted the substrate molecule at the 2-methyl group and not at the homocyclic ring, leading to 2-(1,3-dimethylindolyl)acetaldehyde (**5**).

The product so formed is not stable even in solution and slowly decomposes to give a compound which was not isolated but whose nmr spectrum in carbon tetrachloride [$\delta$ 2.58 (3H, s, Me), 3.99 (3H, s, Me), 9.75 (1H, s, CHO)] and molecular ion (m/e$^+$ 173) suggest the structure of 1,3-dimethyl-2-formylindole (**6**). For comparison, an authentic specimen of the latter was prepared by direct formylation of 1,3-dimethylindole under the same experimental conditions and obtained in almost quantitative yield [nmr in carbon tetrachloride: $\delta$ 2.39 (3H, s, 3-Me), 3.77 (3H, s, N-Me), 6.80-7.45 (4H, m, Ar-H), 9.85 (1H, s, CHO); m/e$^+$ 173].

Thus by this study we can correctly assign the structure of the main formylation product and we suggest that various electrophilic substitutions of 1,2,3-trimethylindole can possibly occur *via* the same mechanism illustrated in the Scheme. However, it should be noted that this pathway is not the only possible way to substituted derivatives. In a previous study on the Vilsmeier-Haack acetylation of 1,2,3-trimethylindole (13) we have demonstrated that the product (mp 123°) already obtained under different conditions (14) was in fact 6-acetyl-1,2,3-trimethylindole [nmr in dimethylsulfoxide-$d_6$: $\delta$ 2.16 (3H, s, 3-Me), 2.32 (3H, s, 2-Me), 2.56 (3H, s, COMe), 3.68 (3H, s, N-Me), 7.34 and 7.56 (2H, dd, 4- and 5-H, $J_{4,5}$ = 8 Hz), 7.95 (1H, s, 7-H)].

Therefore it appears that *ipso* attack at C-3 could compete with direct substitution at the homocyclic ring under certain conditions. Probably the greater steric requirements of the electrophilic reagent in the Vilsmeier acetylation renders much slower the *ipso* attack and substitution at C-6 becomes the prevalent reaction. Further extension of this study to other electrophilic reactions of 1,2,3-trimethylindole is planned in the near future.

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