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# Large-scale Laboratory Electrolysis in Organic Systems. III.[1] The Synthesis of α-Methoxyalkylamides. Cyclic Acylimmonium Precursors

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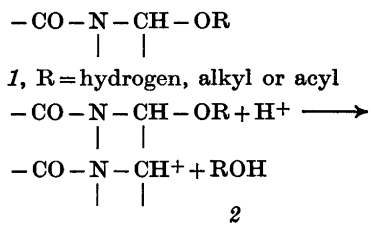
α-Methoxyalkylamides have been synthesized by anodic oxidation of *N*-formyl derivatives of amines, including pyrrolidine, piperidine, azacycloheptane, morpholine, piperazine and others. The methoxy compounds are of synthetic interest in electrophilic amidoalkylation as well as for the preparation of vinylamides.

α-Hydroxy-, alkoxy- and acyloxyalkylamides (*1*) are useful intermediates for synthetic purposes since they act as precursors for acylimmonium ions *2* by heterolytic cleavage of the carbon-oxygen bond under acidic conditions. They are important starting materials in electrophilic amidoalkylation reactions [2] and serve well for the synthesis of vinylamides [3–6] (Scheme 1). In a recent communication it was shown that *N*-acetoxymethyl-*N*-methylformamide reacts with arenes in the presence of trifluoroacetic acid yielding amidoalkylated products in high yield.[7]



*1*, R = hydrogen, alkyl or acyl

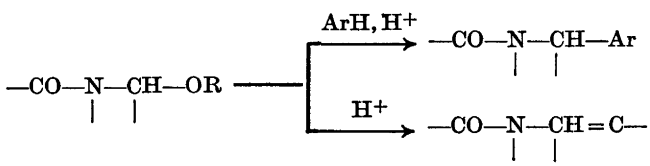


*2*

Alkoxylated or acyloxylated *N*,*N*-dialkylamides have been prepared in a simple anodic oxidation process.[8–11] This reaction has now been extended to other methoxyamides (*1*, R = $CH_3$), in particular those where the nitrogen atom is part of a ring system. Amidoalkylation of arenes with such reagents gives rise to arenes substituted by a saturated heterocyclic ring.[6] Catalytic hydrogenation of such products should possibly cleave the heterocyclic ring yielding ω-aminoalkylarenes.

## RESULTS

Anodic oxidation of *N*-formylated alicyclic amines in methanol containing tetrabutylammonium tetrafluoroborate as the supporting electrolyte was carried out in the concentric capillary gap cell previously described.[1] The results are summarized in Table 1. Besides the cyclic substrates some other amides were also studied. The high yields of products and the simplicity of operation make these reactions



*Scheme 1.*

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*Table 1.* Anodic methoxylation of amides (1 M) in 0.02 M $Bu_4NBF_4$/MeOH ($I = 50$ A, $U = 15-20$ V, $t = 30$ °C).

| Substrate | MeOH/ dm³ | Charge passed/ F mol⁻¹ | Product | Yield g | Yield % [a] | B.p. °C/mmHg |
|---|---|---|---|---|---|---|
| *N*-Formylpyrrolidine | 4 | 8.4 | *N*-Formyl-2-methoxypyrrolidine | 500 | 97 | 77–80/1.5 |
| *N*-Formylpiperidine | 4 | 8.4 | *N*-Formyl-2-methoxypiperidine | 545 | 95 | 69–75/1 |
| *N*-Formylazacycloheptane | 2 | 4.2 | *N*-Formyl-2-methoxyazacycloheptane | 300 | 96 | 102–105/4 |
| *N*-Formylmorpholine | 4 | 8.4 | *N*-Formyl-3-methoxymorpholine | 533 | 92 | 93–97/0.2 |
| *N,N'*-Diformylpiperazine | 3.5 | 7.7 | *N,N'*-Diformyl-2-methoxypiperazine | 548 | 91 | 170–174/0.8 |
| *N*-Methylpyrrolidone | 4 | 8.0 | 4-Methoxy-*N*-methylpyrrolidone [b] | 492 | 88 | 66–70/1 |
| *N*-Formyltetrahydroisoquinoline | 0.5 | 1.05 | *N*-Formyl-1-methoxytetrahydroisoquinoline | 57 | 60 | 84 [c] |
| *N,N*-Diethylformamide | 1.5 | 4.0 | *N*-Ethyl-*N*-(1-methoxyethyl)-formamide | 175 | 89 | 76–77/12 |
| *N,N*-Diethylacetamide | 1 | 2.5 | *N*-Ethyl-*N*-(1-methoxyethyl)-acetamide | 121 | 84 | 82–86/12 |
| *N,N*-Diisopropylformamide | 1 | 17.3 | *N*-Isopropyl-*N*-(1-methoxy-1-methylethyl)formamide | 38 | 24 | 67–69/0.8 [d] |

[a] Material yield. [b] Contains 8 % of *N*-methoxymethylpyrrolidone. [c] M.p. [d] M.p. 66 °C.

synthetically useful. To our knowledge, no other convenient method is available for the synthesis of methoxylated amides. The methoxy compounds, with the exception of the methoxylated *N,N*-diethylamides,[11] have not been reported before.

We also attempted to prepare the corresponding acetoxylated amides but failed. This was probably due to the sensitivity of these compounds to the acidic conditions employed (the oxidations were run in acetic acid containing tetrabutylammonium tetrafluoroborate) resulting in elimination and further reactions of the enamides formed. A low yield of the product was obtained in the oxidation of *N,N*-diisopropylformamide in methanol. Since the product contains a tertiary α-methoxyalkyl group it is evident that this compound should be more sensitive to the reaction conditions (elimination) than the other methoxylated compounds. Therefore, the low yield of the product is not surprising.

## EXPERIMENTAL

The starting materials were prepared by conventional formylation procedures (reactions between amines and formamide, ethylformate or acetic formic anhydride, respectively).[12,13] *N*-Methylpyrrolidone and *N,N*-diethylacetamide were of commercial quality. The anodic reactions were carried out as previously described.[1] Results and reaction conditions are given in Table 1. The reaction mixtures were worked up by evaporation of the solvent followed by distillation *in vacuo*. In the reaction with *N*-formyltetrahydroisoquinoline the product was isolated by filtering the precipitate from the cooled reaction mixture. A second crop was obtained by concentrating the filtrate, followed by cooling.

The purity of the products were checked by GLC (2 m × 0.3 cm 5 % NPGS on Chromosorb W column, Perkin-Elmer Model 880 Gas Chromatograph) and was found to be better than 95 % in all cases. The impurities consisted of starting material, enamide (elimination product) and bis-methoxylated material. The products were identified by their mass (LKB 9000 mass spectrometer at 70 eV) and $^1H$ NMR spectra (in $CDCl_3$; Jeol MH 100). These data were in complete agreement with the proposed structures.

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