

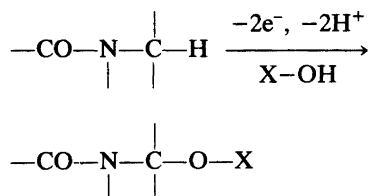
Short Communications

1-Formyl-5-methoxyproline Methyl Ester. Electrochemical Preparation and Use as Amidoalkylation Reagent

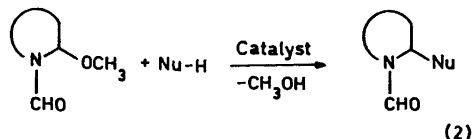
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The α -functionalization of amides by electrochemical oxidation in nucleophilic solvents (usually acetic acid or methanol, eqn. 1) has been



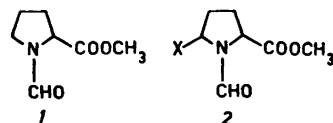
subjected to extensive studies by numerous researchers in recent years.¹⁻⁸ One of the most interesting applications was found in the anodic methoxylation of cyclic amides^{4,5,7,8} and their subsequent use in reactions with nucleophiles, providing a new approach to heterocyclic systems (eqn. 2). In most cases these reactions have been



applied to unsubstituted or alkyl-substituted cyclic amides or carbamates.

In this report we introduce the cyclic α -amino acid derivative **1** as a substrate for anodic

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2a: X = -OCH₃

2b: X = -CH(COOCH₃)₂

2c: X = 2,4,6-trimethylphenyl

methoxylation and describe a simple method for the preparation of proline derivatives exemplified by the reaction of **2a** with dimethyl malonate and mesitylene. The latter compounds were chosen because of their documented high reactivity in amidoalkylation reactions.¹⁰⁻¹¹

The oxidation of **1** was carried out in methanol solution at a platinum anode. The course of the reaction was checked by GLC analysis and the theoretical amount of charge for complete conversion of the starting material into products (2 F/mol) was exceeded by 30 % at the end of the electrolysis. According to GLC analysis the starting material was completely consumed and as the only detectable product the diastereomeric compound **2a** was formed in high yield. After work-up, one of the diastereomers crystallized and could be isolated. MS and NMR analyses were in agreement with the anticipated structure and NMR analysis confirmed the presence of only one isomer. The relative configuration of this isomer has not been established. The remaining liquid portion of the product proved to be a mixture of two isomers.

Due to poor separation on GLC analysis only a rough estimate of the isomeric ratio (1.5:1 in favour of the solid product) could be made. The isomeric mixture was satisfactorily identified as pure **2a** by GLC-MS and NMR analyses. The amidoalkylation of dimethyl malonate was carried out with AlCl₃ as catalyst in dichloromethane solution (see Experimental), a procedure successfully applied to electrophiles with similar structure, e.g. 2-methoxy-1-pyrrolidinedicarboxaldehyde.¹⁰ In the reaction of **2a** with dimethyl malonate, a 49 % yield of crude **2b** was obtained after distillation. The distillate was found to contain 15 % of a by-product. Fortunately **2b** slowly crystallized and could be isolated

for proper identification by NMR analysis. GLC analysis indicated the formation of only one isomer, although MS analysis of the by-product, with 228 as the heaviest fragment of reliable intensity, showed a close relation to *2b*. However, most likely the by-product was formed from hydrolysis and decarboxylation of the malonic acid moiety of the product. This reaction has never been observed by us in similar reactions.

The reaction conditions applied in the reaction with mesitylene were based on our previous results from amidoalkylation of aromatic compounds.¹¹ Except in the case of highly activated aromatic compounds such as alkoxybenzenes,⁹ these reactions were best carried out in a large excess of the nucleophile and with a strong Lewis acid such as AlCl_3 as catalyst. The details for the amidoalkylation of mesitylene are given in the Experimental section. The product, *2c*, isolated in 46 % yield after distillation, was found to be a mixture of the diastereoisomers in a 3.5:1 ratio.

Preparation of 2-methoxypyrrolidine derivatives from anodic methoxylation of proline derivatives involving concomitant decarboxylation has previously been reported by Iwasaki *et al.*^{14,15}

Experimental. GLC analyses were performed using a Hewlett-Packard HP-5830 instrument equipped with a 1.5 m \times 3 mm 5 % OV-17 on Chromosorb W column. ^1H NMR spectra were recorded on a Jeol 100 Mz spectrometer using CDCl_3 as solvent. MS analyses were performed on a Finnigan 4021 instrument at 70 eV.

Esterification and formylation of *l*-proline. Methanol (500 ml) was saturated with hydrogen chloride and *l*-proline (0.4 mol) was added. After 24 h at room temperature the solvent was removed by evaporation *in vacuo* and another portion of methanol (500 ml), saturated with hydrogen chloride was added. The above procedure was repeated and a third portion of acidic methanol was added. Finally, methanol and most of the hydrochloric acid were removed by evaporation *in vacuo* and the residue was neutralized with 1 M sodium methoxide/methanol (phenolphthalein). Most of the methanol was distilled off and an excess methyl formiate (75 ml) was added. The solution was refluxed for 24 h and, after filtration, the product was distilled at reduced pressure using a Claisen apparatus. Yield 39.7 g (63 %), b.p. 102–112 $^\circ\text{C}/0.5$ – 0.7 mmHg.

Anodic methoxylation. In a water-jacketed cell compound *1* (0.109 mol) was dissolved in methanol (150 ml) together with Bu_4NBF_4 (1 g, 0.02 M solution). The cell was fitted with a platinum foil (50 cm^2) and a central graphite rod and the electrolysis was performed at constant current (2.5 A, 50 mA/cm^2) with Pt as anode and

continuous stirring. After 2.6 F/mol the starting material was consumed (GLC analysis) and the solvent was removed by evaporation *in vacuo*. The crude product was finally distilled in a Claisen flask at reduced pressure. After distillation, part of the product crystallized and was filtered off and washed with ether. The ether was removed from the filtrate by evaporation *in vacuo*. The residual oil was a pure mixture of two isomers. Yield (solid product) 5.7 g (28 %), m.p. 110–113 $^\circ\text{C}$ and 11.7 g (57 %). MS *m/e* (% rel. int.), solid isomer: 187 (very small, M), 172 (2, M- CH_3), 157 (4), 156 (3, M- OCH_3), 155 (4), 128 (25, M- COOCH_3), 100 (8), 96 (7, $\text{C}_5\text{H}_6\text{NO}$), 68 (100, $\text{C}_4\text{H}_6\text{N}$) and (other isomer): 188 (1, M+1), 187 (0.5, M), 172 (3, M- CH_3), 157 (3), 156 (2, M- OCH_3), 155 (3), 128 (44, M- COOCH_3), 100 (36), 96 (9, $\text{C}_5\text{H}_6\text{NO}$), 68 (100, $\text{C}_4\text{H}_6\text{N}$). ^1H NMR (solid isomer; ratio=ratio of conformational isomers due to restricted rotation of the amide bond): 1.70–2.47 (4 H, m), 3.36 and 3.38 (3H, 2 s in the ratio 6:1), 3.74 and 3.78 (3 H, s in the ratio 6:1), 4.47 (1 H, t with further splitting, *J* 8 Hz approx.), 5.06 and 5.44 (1 H, 2d in the ratio 6:1, *J* 4 Hz), 8.26 and 8.38 (1 H, 2 s in the ratio 1:6). The NMR spectrum of the isomeric mixture showed similar features, though more complex, and is not listed.

Amidoalkylation of dimethyl malonate. Compound *2a* (0.025 mol of the isomeric mixture) and dimethyl malonate (0.025 mol) in dichloromethane (5 ml) were added to a stirred mixture of AlCl_3 (0.035 mol) in dichloromethane (20 ml). The course of reaction was checked by GLC analysis and after 15 h additional catalyst and dimethyl malonate (0.025 mol of each) were introduced. The yield was further improved by two more additions of dimethyl malonate (2×0.025 mol) within 48 h and after a total reaction time of 70 h most of compound *2a* was consumed and the reaction mixture was subjected to work-up. Water (50 ml) was added and the phases were separated and the aqueous layer was extracted twice with dichloromethane. The organic layers were combined and washed with water and sodium hydrogen carbonate solution before being dried over magnesium sulfate and evaporated *in vacuo*. The residuary oil was distilled at reduced pressure using a Kugelrohr apparatus (140–160 $^\circ\text{C}/0.2$ mmHg) and the distillate was found to be contaminated by 15 % of a by-product (see previous section). The main product slowly solidified and was recrystallized from ethanol (3 ml). Yield 3.51 g (distillate) and 1.29 g (19 %) (after recrystallization), m.p. 82–89 $^\circ\text{C}$. MS *m/e* (% rel. int.): 287 (2, M), 258 (3, M- CHO), 256 (2, M- OCH_3), 200 (13, M-($\text{CO}+\text{COOCH}_3$)), 168 (4, M-(COOCH_3+

HCOOCH₃), 156 (3, M-CH(COOCH₃)₂), 133 (8), 128 (15, C₄H₇NCOOCH₃), 68 (100, C₄H₆N). ¹H NMR: 1.81–2.15 (4 H, m), 3.70–3.79 (9 H, 6 s), 4.28–4.87 (3 H, m), 8.30 and 8.37 (1 H, 2 s).

Amidoalkylation of 1,3,5-trimethylbenzene. Compound **2a** (0.295 mol of the isomeric mixture) was dissolved in 1,3,5-trimethylbenzene (10 ml) and added slowly to a stirred mixture of AlCl₃ (0.059 mol) in 1,3,5-trimethylbenzene (30 ml). During and after the addition of **2a** a sticky mass of an insoluble dark red complex was formed. In order to increase the solubility, dichloromethane (40 ml) was added. The main part of the oil was dissolved and the mixture was vigorously stirred for 7 h before being worked up as described for the reaction with dimethyl malonate. GLC analysis indicated 10 % of the starting material still to be present. After evaporation of the solvents *in vacuo* at 100 °C, the crude oil was distilled on a Kugelrohr apparatus at reduced pressure. According to GLC analysis the isomeric product was of high purity. Yield 3.75 g (46 %), b.p.: the product was collected at 130–160 °C at 0.2 mmHg. Ms *m/e* (% rel. int.): 275 (6 M), 260 (4, M-CH₃), 257 (7), 246 (3, M-CHO), 216 (20, M-COOCH₃), 161 (37), 159 (18), 156 (32, M-C₆H₂(CH₃)₃), 128 (84, C₄H₇NCOOCH₃), 68 (100, C₄H₆N) and (other isomer) 275 (2, M), 260 (2, M-CH₃), 230 (3), 216 (38, M-COOCH₃), 171 (32), 159 (36), 156 (41, M-C₆H₂(CH₃)₃), 128 (100, C₄H₇NCOOCH₃), 68 (72, C₄H₆N). ¹H NMR: 1.99–2.56 (4 H, m), 2.24 (6 H, s), 2.42 (3 H, s), 3.75 (3 H, s), 4.56 (1 H, t, J 7.5 Hz), 5.37 (1 H, t, J 8 Hz), 6.85 (2 H, s), 7.81 and 7.85 (small) (1 H, 2 s).

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