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REDUCTION BY A MODEL OF NAD(P)H. XIX. MIMESIS FOR THE REACTION WITH GLUTAMATE DEHYDROGENASES

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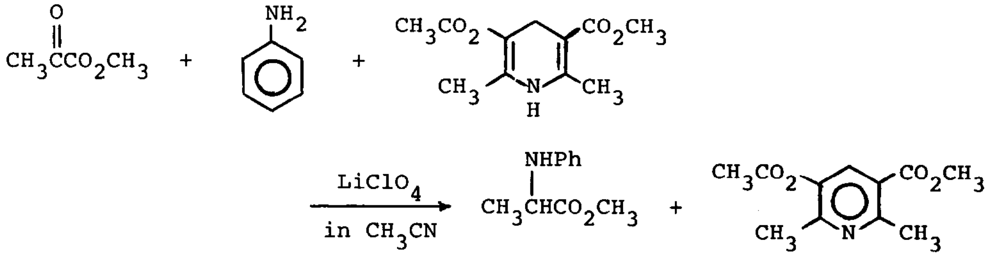
Glutamate dehydrogenases catalyze an interconversion between α-ketoglutarate and L-glutamate by the aid of NADH.[1] Enzymes in this group are very interesting

$$\alpha\text{-Ketoglutarate} + \text{NADH} + NH_4^+ \rightleftharpoons \text{L-Glutamate} + \text{NAD}^+ + H_2O$$

because they provide a rout to incorporate inorganic nitrogen into an organic molecule——amino acid. In the course of our research on bio-mimetic reactions of NAD(P)H, we studied a model reaction for NADH-dependent syntheses of amino acids from α-keto acids. This paper describes a one-step synthesis of an α-amino ester derivative from the corresponding α-keto ester by consecutive imination and reduction. It is well documented that the bio-mimetic reduction of imines is susceptible to acid-catalysis.[2-5]



Methyl pyruvate (530 mg, 5 mmol) was allowed to react with aniline (465 mg, 5 mmol) and Hantzsch ester (1.575 g, 7 mmol) in the presence of lithium perchlorate (1.06 g, 10 mmol) in acetonitrile (100 ml) at a room temperature for 4 days in the dark. Water (50 ml) was added to the solution and the mixture was extracted with benzene (30 ml x 3). The organic layer was dried on sodium sulfate and the solvent was evaporated *in vacuo*. The yield of product, N-phenylalanine methyl ester, was found to be 52% on vpc (PEG, 180°C; N_2, 0.4 kg/cm^2; O,O'-diisoamyl *p*-hydroquinone as an internal standard). The residue was chromatographed on a column of silica gel with an eluent of hexane-ethyl acetate (4:1 v/v) mixture yielding 630 mg (35% yield) of the pure product. The nmr, ir, and mass spectra of the product were identical to those of the authentic sample. Elemental analyses also gave satisfactory result. Neither methyl lactate nor methyl pyruvate was detected on vpc after the reaction. Thus, lithium perchlorate catalyzes only the reduction of imino ester but not of the keto ester.[6,7] Although lithium ion cannot be substituted by a bivalent metal ion such as magnesium or zinc ion because the latter catalyzes the reduction of α-keto esters,[6,7] ammonium ion is as good catalyst as lithium ion for the present reaction. Unfortunately, however, an attempt to prepare an amino ester from ammonia or an alkylamine was unsuccessful, because the keto-imino equilibrium with these reagents is much shifted toward the keto-form in acetonitrile.

No reaction took place with 1-benzyl-1,4-dihydronicotinamide (BNAH). Since it is confirmed that amide anion, similarly to other bases,[8,9] can reduce BNA^+ or its analog, there is no doubt, for the reduction with BNAH, that the equilibrium between reactants and products is favorable to the former. The reduction with Hantzsch ester affords uncharged products, and the reaction is free from the annoyance of equilibrium.

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