

Asymmetric Autocatalytic Mannich reaction in water and its implication in prebiotic chemistry

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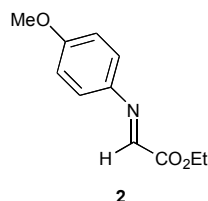
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Experimental Section

General Information: Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Flash column chromatography was performed using 200-300 mesh silica gel. ^1H NMR spectra were recorded on Varian Unity 400 (400 MHz) spectrophotometers. Chemical shifts are reported in ppm from the solvent resonance as the internal standard (CDCl_3 : 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = single, d = doublet, t = triplet, m = multiplet) and coupling constants (Hz).

^{13}C NMR spectra were recorded on Varian Unity 400 (100 MHz) with complete proton decoupling (CDCl_3 : 77.23 ppm). Chiral HPLC was performed using a Varian 9012 pumping system and Varian 9050 UV detector series with a chiral column (Chiralcel OD, 0.46cm (ϕ x 25cm, Daicel Chemical Ind., Ltd.).

Procedure for the synthesis of *N*-PMP-imino ethyl glyoxylate (**2**):¹



Ethyl glyoxalate (8.14 mL, 50% sol in toluene, 40 mmol) was dissolved in dichloromethane (150 mL) and a solution of *p*-anisidine (4.92 g, 40 mmol) in dichloromethane (50 mL) was added slowly. The reaction mixture was stirred at room temperature for 30 min and pre-activated 4 Å molecular sieves were added. After stirring for an additional 1 h, the mixture was filtered and the filtrate evaporated *in vacuo* to give the *title compound*, analytically pure, as a yellow oil (7.80 g, 95%). ^1H NMR (400 MHz, CDCl_3) δ = 7.95 (1H, s, $\text{HC}(\text{N})$), 7.36 (2H, d, J = 8.8 Hz, ArH), 6.94 (2H, d, J = 8.8 Hz, ArH), 4.44 (2H, q, J = 7.2 Hz, CH_2CH_3), 3.85 (3H, s, OCH_3), 1.41 (3H, t, J = 7.2 Hz, CH_2CH_3).

General procedure for the synthesis of (2*S*,1'*S*)-Ethyl-2-(*p*-methoxyphenylamino)-2-(2-oxocyclohex-1-yl)-acetate.¹

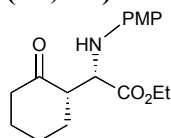
The reactions were performed in a test tube with a cap. *N*-PMP-protected-imino ester (1.0 mmol, 1.0 equiv) was dissolved in DMSO (1.0 mL) and cyclohexanone (2.0 mmol, 2.0 equiv) was added to the solution, followed by L-proline (20 mol %). The mixture was stirred at room temperature (20 °C) for 4 h and then quenched with

1. (a) W. Notz, S-I. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka, C. F. Barbas III, *Adv. Synth. Catal.* 2004, **356**, 1131; (b) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* 2005, **3**, 84. (c) H. Zhang, M. Mifsud, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* 2006, **128**, 9630.

saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a residue, which was purified by flash column chromatography. The enantiomeric excess of the *syn*-product was determined by chiral-phase HPLC analysis.

The Mannich adducts *syn*-**3** and *anti*-**3** are known products, and were characterized by comparison with literature data as shown below.

(2*S*,1'*S*)-Ethyl-2-(*p*-methoxyphenylamino)-2-(2-oxocyclohex-1-yl)-acetate.^{1b}



(2*S*,1*S*)-**3**

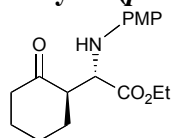
Purified using flash column chromatography (EtOAc–heptane, 1 : 4) to give the *title compound* as a yellow oil (99.1 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ = 6.70–6.79 (4H, m, ArH), 4.23 (1H, d, *J* = 5.2 Hz, CHNH), 4.14 (2H, m, OCH₂CH₃), 3.75 (3H, s, OCH₃), 2.82 (1H, q, *J* = 6.0 Hz, CHCHNH), 2.46–1.66 (8H, m, chex-H), 1.22 (3H, t, *J* = 6.9 Hz, CH₂CH₃).

HPLC analysis Chiralcel OD (Hexane/ *i*-PrOH = 95/5, 1.0 mL/min, 254 nm, 20 °C) *t*_R (major) 16.2 min and *t*_R (minor) 15.2 min, ee: 98%;

Synthesis of (±)-*anti*- and (±)-*syn*-Mannich products.^{1c}

Racemic standards of the Mannich products were synthesized as a racemic mixture of the diastereomers and enantiomers using pyrrolidine-trifluoroacetic acid as catalyst. Racemic standards of the *syn*-Mannich products were synthesized by using (±)-proline as catalyst.

Ethyl-2-(*p*-methoxyphenylamino)-2-(2-oxocyclohex-1-yl)acetate, (±)-*anti*-3**.**



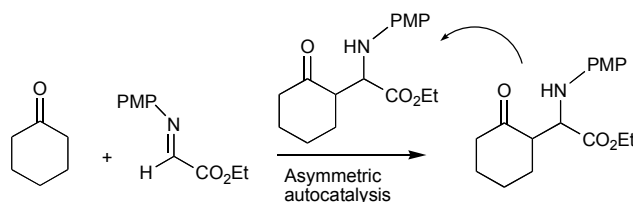
(±)-*anti*-**3**

¹H NMR (400 MHz, CDCl₃) δ = 6.81 (2H, m, ArH), 4.24 (m, 1H, CHNH), 4.15 (2H, m, OCH₂CH₃), 3.76 (3H, s, OCH₃), 3.15 (1H, m, CH₂CHCO), 2.50–2.25 (2H, m, CH₂CH₂CO), 2.17–1.85 (4H, m, CH₂), 1.82–1.67 (2H, m, CH₂), 1.23 (3H, t, *J* = 7.2 Hz, OCH₂CH₃).

HPLC analysis Chiralcel OD (Hexane/ *i*-PrOH = 95/5, 1.0 mL/min, 254 nm, 20 °C) *t*_R 12.7 min and *t*_R 14.5 min

General procedure for the Autocatalytic Mannich reaction

The yields are given as after subtraction of the initially added catalytic product.



Reaction in organic solvent: The following procedure for the reaction in DMF is representative for reactions carried out in organic solvents.

N-*p*-Methoxybenzyl- α -iminoglyoxalate **2** (103.5 mg, 0.5 mmol) was dissolved in DMF (0.4 mL). Cyclohexanone (100 μ L, 1 mmol) was added to this solution followed by Mannich-adduct (2*S*,1'*S*)-**3** with 98% ee (15.25 mg, 10 mol%). The resulting mixture was stirred at room temperature (20 °C) for 18 h. After this time, the mixture was quenched with saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a residue, which was purified by flash column chromatography using ethyl acetate and heptane (1:4) as eluent to give the *title compound* as a yellow oil 56 mg (0.19 mmol, 38% yield). The diastereomeric ratio was determined by ¹H NMR of the crude product (see table 1 in article).

Observation of autocatalysis by ¹H-NMR. The reaction was performed as described above in CDCl₃ (0.4 ml). At 30min interval samples were withdrawn (10 μ L), and transferred to an NMR tube containing 0.7 mL CDCl₃. Within 10 min, NMR measurements were performed.

Reaction in water: The following procedure for the reaction in water is representative for reactions carried out in aqueous media.

N-*p*-Methoxybenzyl- α -iminoglyoxalate **2** (103.5 mg, 0.5 mmol) was added to cyclohexanone (100 μ L, 1 mmol) in water (0.4 mL) followed by Mannich-adduct (2*S*,1'*S*)-**3** with 98% ee (30.50 mg, 20 mol %). The resulting emulsion (two phase mixture) was stirred at room temperature (20 °C) for 5 h. After this time, saturated aqueous ammonium chloride (1 mL) was added to the mixture and extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a residue, which was purified by flash column chromatography using ethyl acetate and heptane (1:4) as eluent to give the *title compound* as a yellow oil 65 mg (0.21 mmol, 43% yield). The diastereomeric ratio was determined by ¹H NMR of the crude product (see table 1 in article).