

Reactivity of Methyl Mandelate-Ti(IV)-Enediolate: Oxidative Homocoupling versus Aldol and Direct Mannich Type Syn-diastereoselective Condensation

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Supporting Information

Contents:

Experimental Section

S-2 to S-4

General All reactions were performed under N₂. An anhydrous TiCl₄ solution (1.0 M) in CH₂Cl₂ was used for methods *i-v*. ¹H NMR spectra were recorded in CDCl₃ on a AC-250 MHz and diastereoselectivity were determined by ¹H NMR analyses of the crude reaction mixtures.

Method i. Procedure for the oxidative coupling of 2 (Table 1, entry 4). Dropwise addition of the TiCl₄ solution (2 mmol, 2 mL) to a solution of **2** (2 mmol) in CH₂Cl₂ (10 mL), kept at 0°C under N₂, gave rise a yellow precipitate (indicative of **2**-Ti(IV) complexation). After 15 min, triethylamine (TEA, 6 mmol) was slowly added (5 min) through a syringe dipping the needle into the solution. The yellow precipitate dissolved and the blue solution (indicative of Ti(III) formation) was stirred at r.t. for additional 30 min. A saturated NH₄Cl solution was then added to the mixture and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. **3** was recovered in quantitative yield and the meso/*dl* ratio, 83:17, was determined by ¹H NMR analysis of the crude reaction mixture.

Dimethyl 2,3-dihydroxy-2,3-diphenylbutanedioate (3). The diastereomers were separated by flash column chromatography (hexane/EtOAc, 6.5/3.5). meso-isomer (less polar) was recrystallized from ethyl ether to give colorless square crystals of mp 153 °C (lit. mp 151-3 °C); ¹H NMR (CDCl₃) δ 3.85 (6H, 2OCH₃, s), 5.0 (2H, 2OH, s, D₂O exch.), 7.0-7.2 (10 H, Ph H, m). dl-isomer (more polar) was recrystallized from CH₃COCH₃/hexane to give white crystals of mp 120-1 °C (lit.¹ mp 119-21 °C); ¹H NMR (CDCl₃) δ 3.79 (6H, 2OCH₃, s), 5.5 (2H, OH, br, D₂O exch.), 7.0-7.5 (10 H, Ph H, m). Juday, R. E. *J. Org. Chem.* 1958, 23, 1010.

Method ii. Procedure for the oxidation of 2 to 1 (Table 1, entry 7). Dropwise addition of TEA (6 mmol) to a solution of **2** (2mmol) in CH₂Cl₂ (10mL), kept at 0°C under N₂, was followed after 10 min. by slow addition (5 min) of a TiCl₄ solution (2 mmol, 2 mL). The resulting blue solution was stirred for additonal 30 min at r.t. Work up as above. ¹H NMR analysis of the crude reaction residue gave methyl phenylglyoxylate **1** (30%), **3**-meso (14%) and the starting **2** (56%).

Method iii. Procedure for Aldol condensation of 2 (Table 2, entry 2). Dropwise addition of the TiCl_4 solution (2 mmol, 2 mL) to a solution of **2** (2 mmol) and 4-bromobenzaldehyde (2 mmol) in CH_2Cl_2 (10 mL), at 0°C under N_2 , afforded a yellow precipitate. After 15 min, TEA (4 mmol) was slowly added (6 min) through a syringe dipping the needle into the solution. The precipitate dissolved and the yellow solution was stirred at r.t. for additional 30 min. Work up as above afforded **4** in quantitative yield. The syn/anti ratio, 83:17, was determined by ^1H NMR analysis of the crude reaction mixture.

Methyl 2,3-dihydroxy-2-phenyl-3-(4-bromophenyl)propanoate (4). For spectroscopic data of both isomers and X-ray structure of **4-syn**. Clerici, A.; Clerici, L.; Malpezzi, L.; Porta, O. *Tetrahedron* **1995**, *51*, 13385-13400.

Method iv. Procedure for Aldol condensation of 2 (Table 2, entry 5). Dropwise addition of TEA (4 mmol) to a solution of **2** (2 mmol) and 4-bromobenzaldehyde (2 mmol) in CH_2Cl_2 (10 mL), kept at 0°C under N_2 , gave rise to a yellow homogeneous solution. The colour of the solution did not change upon TiCl_4 (2 mmol, 2 mL) dropwise addition (5 min). The reaction mixture was allowed to react for additional 30 min at r.t. Work up and ^1H NMR analysis as above.

Method v. Procedure for direct Mannich type condensation (Table 3, entry 4). The TiCl_4 solution (4 mmol, 4 mL) is added dropwise in 6 min to a well stirred solution of **2** (2 mmol), 4-bromobenzaldehyde (2 mmol), aniline (3 mmol) and TEA (4 mmol) in CH_2Cl_2 (10 mL), kept at r.t. under N_2 . The yellow solution was allowed to react for 2 h at the same temperature. Work up and ^1H NMR analysis as above. The Mannich product **5** could be directly extracted from the aqueous acidic solution (work up as above), whereas the unreacted aniline remained in the aqueous layer.

Methyl 2-hydroxy-2-phenyl-3-(4-bromophenyl)-3-phenylaminopropanoate (5-syn). Flash column chromatography (hexane/EtOAc, 7:3) of the crude residue afforded in the order: imine (traces), unreacted 4-bromobenzaldehyde, **5-syn** (510 mg, 60%) and unreacted **2**.

Recrystallization of **5-syn** from hexane/EtOAc gave pale yellow needles of mp 144-6 °C. ¹H NMR (CDCl₃) δ 3.82 (3H, OCH₃, s), 4.13 (1H, OH, br, D₂O exch.), 4.85 (1H, NH, br, D₂O exch.), 5.20 (1H, CH, s), 6.60 (2H, Ph H, m), 6.67 (1H, Ph H, m), 6.91 (2H, Ph H, m), 7.05-7.15 (4H, Ph H, m), 7.23 (3H, 1Ph H+2Ar H, m), 7.52 (2H, Ar H, m). ¹³C NMR: 53.9, 62.6, 81.4, 114.4, 118.3, 121.2, 125.8, 126.8, 128.1, 129.1, 130.1, 130.2, 130.6, 138.2, 145.9, 174.6. IR (KBr) ν_{max} 3500, 3380, 1720, 1240 cm⁻¹. EIMS (*m/z*) 427-425 (M⁺, < 1), 368-366 (M-CO₂CH₃, < 1), 262-260 (100), 180 (20), 77 (80). Anal. Calcd for C₂₂H₂₀NO₃Br: C, 62.12; H, 4.71; N, 3.29, Found: C, 62.02; H, 4.67; N, 3.25. Crystallographic data (excluding structure factors) for **5-syn** has been deposited with Cambridge Crystallographic Data Centre as supplementary publication N° CCDC 1267/1273. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 (0)1 2233336033 or e-mail: deposit@ccdc.cam.ac.uk).