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Asymmetric Synthesis of (+)- and (-)- 2-(2-Methoxyphenyl)-3,1-benzoxathiane

Angela Bassoli*, Lucio Merlini

Dipartimento di Scienze Molecolari Agroalimentari, Università di Milano, V. Celoria 2, 20133 Milano (Italy)

Clara Baldoli, Stefano Maiorana

CNR-Centro Studio Sintesi e Stereochimica Speciali Sistemi Organici and

Dipartimento di Chimica Organica e Industriale, V. Golgi 19, 20133 Milano (Italy)

Michael G. B. Drew

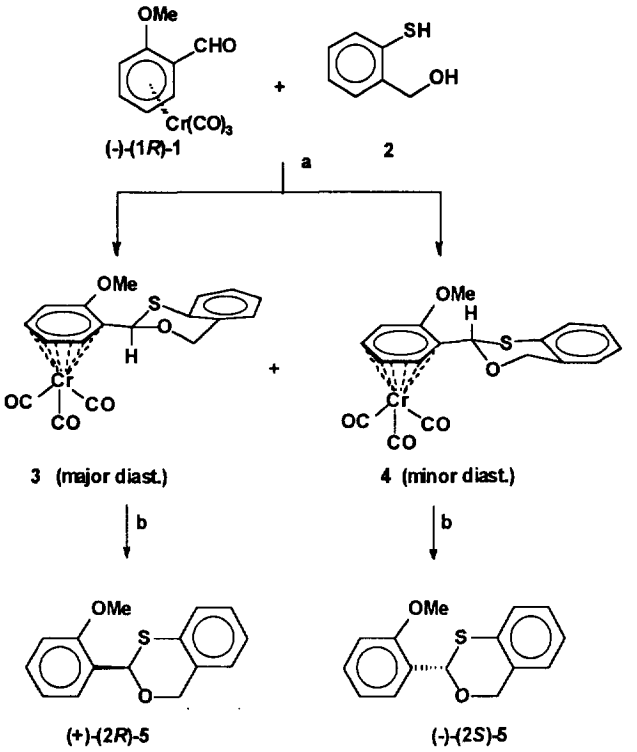
Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, (UK)

Abstract: Enantiomerically pure (-)-(1*R*)-tricarbonyl-(2-methoxybenzaldehyde)chromium reacts with 2-mercaptobenzylalcohol to give the corresponding diastereomeric thioacetal complexes, which are separated and transformed quantitatively into the enantiomerically pure thioacetals (+)- and (-)-**5** by removing the chromium tricarbonyl moiety.

As a part of an ongoing research program we are interested in the synthesis of optically active 2-aryl-3,1-benzoxathianes bearing a stereogenic center at the C2 acetal carbon atom. To our knowledge no stereoselective synthesis has been developed until now for this class of compounds. In contrast with the analogous 1,3-dioxanes, 1,3-oxathianes and dithianes are generally more stable to hydrolytic conditions and also less prone to racemization at least under neutral and basic conditions. Furthermore, these heterocyclic compounds are quite rigid from a conformational point of view, and have thus been used sometimes in diastereoselective reactions [1].

The stereoselective generation of a stereogenic center in a benzylic position is a general target in asymmetric synthesis and has often been successfully achieved using homochiral tricarbonyl (η^6arene)chromium complexes[2]. Chiral complexes of benzaldehyde and acetophenone acetals and ketals have been widely used as protecting groups[3] and for stereoselective transformations at benzylic[4] or *ortho* position[5] of the aromatic ring. Analogous complexed thioacetals and hemithioacetals have never been studied, hence the stereoselective synthesis of these compounds is both an interesting and promising target. Racemic tricarbonyl-(2-methoxybenzaldehyde)chromium **1**[3,6] (1 mmol) reacted with 2-mercaptobenzylalcohol **2**[7] (1 mmol, refluxing benzene with Dean-Stark trap, catalytic amounts of p-toluenesulfonic acid) to give a mixture of the diastereomeric thioacetal complexes (±)-**3** and (±)-**4**. (Scheme 1). The d.e. ranges from 30% to 99% depending on the reaction time, the best values obtained when the aldehyde was added rapidly to the refluxing mixture of the thiol **2** and the catalyst in benzene (conversion complete after 5 minutes).

Notably, the diastereoisomeric thioacetals (±)-**3** and (±)-**4** were easily separated by flash chromatography (hexane/diethylether 6:4 v/v). Their structures differ in the ^{1}H-NMR spectra for the position of the acetal hydrogen and the different pattern of the AB system of the CH_2 group[8].



Scheme 1 a: Benzene, Dean-Stark apparatus, PTSA b:CH_2Cl_2, air, sunlight

The major diastereoisomer **3** was submitted to X-ray analysis[9] to establish the relative configuration of the stereogenic centers (Fig 1); the configuration of this compound is *R*R**, as expected from the *exo* nucleophilic attack of the sulfur atom on the formyl group, disposed in the preferred conformation *anti* to the *o*-methoxy group.

Racemic **3** and **4** were submitted to standard photolytic decomplexation[10] to give the thioacetal (±)-**5** in quantitative yield.

The same sequence was then applied to enantiomericaaly pure (-)-(1*R*)-tricarbonyl-(2-methoxybenzaldehyde) chromium **1**[3,6] (0.1 mmol), which reacted with the thiol **2** (0.1 mmol) to give the diastereomeric mixture of *R,R*-**3** (70%) and *R,S*-**4** (12%) complexes. Pure **3** and **4** were isolated by flash chromatography and shown to be enantiomerically pure (e.e > 98%) by chiral HPLC[11].

The major diastereoisomer **3** was decomplexed to give the optically active (+)-2-(2-methoxyphenyl)-3,1-benzoxathiane (+)-**5**[12]in quantitative yield [98% e.e. by HPLC; $[\alpha]_D$ = +139 (c 0.076, $CHCl_3$)]. The enantiomer (-)-**5** was obtained by the same reaction from **4** (95% e.e. by HPLC)[13].

It is noteworthy that no appreciable racemization of the acetal stereogenic center occurs during decomplexation, owing to the very mild conditions.

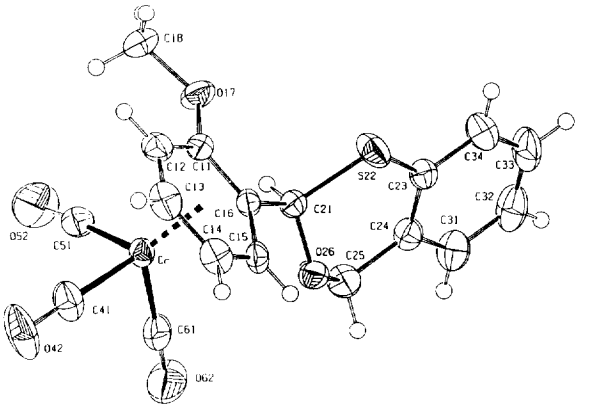


Fig. 1- The structure of **3**
Ellipsoid shown at 50% probability. Hydrogens shown as small circles of arbitrary radii.

The assignment of the absolute configuration *R* and *S* to (+)- and (-)-**5** respectively follows from the knowledge of the absolute configuration of the aldehyde (-)-(1*R*)-**1** and of the relative configuration of the two stereogenic centers in compounds **3** and **4**.

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8. Compound **3**: yellow needles, m.p. 155 (dec); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.80 (3H, s, OMe); 4.92 (1H, t, J=6 Hz), 5.07 (1H, d, J=6 Hz), 5.51 (1H, t, J=6 Hz) and 5.94 (1H, d, J=6 Hz), $Cr(CO)_3$(arom. H); 5.08 (2H, AB, CH_2); 6.12 (1H, s, CH); 7.0-7.3 (4H, m,ar.). MS (EI): m/z (%) 394 (5, M^+), 338 (8), 310 (43), 295 (29), 173 (100). IR ($CHCl_3$, cm^{-1}) 1870, 1960. Compound **4**: yellow solid, m.p. 138; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.80 (3H, s, OMe); 4.90 (1H, t, J=6 Hz), 4.94 (1H, d, J=6 Hz), 5.61 (1H, t, J=6 Hz) and 6.20 (1H, d, J=6 Hz), $Cr(CO)_3$(arom. H); 4.99 (1H, d, J=15 Hz, H-2a(b)); 5.10 (1H, d, J=15 Hz, H-2b(a)); 6.28 (1H, s, CH); 6.9-7.3 (4H, m, ar). MS (EI): m/z (%) 394 (10, M^+), 338 (42), 310 (94), 295 (55), 173 (100). IR ($CHCl_3$, cm^{-1}) 1880, 1960.

9. Crystals were obtained from benzene-hexane. Crystal data for **5**.½ benzene were collected with MoKα radiation using the MARresearch Image Plate System. The crystal was positioned at 75 mm from the Image Plate. 95 frames were measured at 2° intervals with a counting time of 2 mins. Data analysis was carried out with the XDS program. Crystals of formula $C_{21}H_{17}CrO_5S$, M=433.4 belonged to the triclinic spacegroup P-1, a=6.980(7), b=7.860(7), c=19.22 (2) Å, α =95.79(1), β=90.50(1), γ=107.01(1)°, V=1000.2 $Å^3$, Z=2, 3114 independent reflections were measured. The structure was solved using direct methods with the Shelx86 program. The non-hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structure was then refined using Shelxl to R1 of 0.0525 and wR2 of 0.2071. Coordinates have been deposited at the Cambridge Crystallographic Data Centre.

10.CH_2Cl_2, r.t., air, sunlight.

11. Column Chiralcel OD (Daicel), hexane/iPrOH 90:10 (v/v), flow 1ml/min ; UV detector, λ 254 nm.

12. White solid, m.p. 60°. ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.8 (1H, s, OMe); 5.1 (2H, s, CH2); 6.5 (1H, s, CH); 6.9-7.5 (8H, m, arom). MS (EI): m/z (%) 258 (8), 215 (5), 135 (15), 122 (100).

13. An analytical sample of compound (-)-**5** had m.p, ^{1}H-NMR and MS spectra identical to those of (+)-**5**.

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