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Resolution of 2-Azol-1-ylsuccinic Esters by Enantioselective Inclusion Methodology

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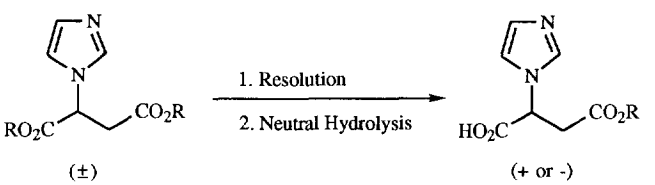
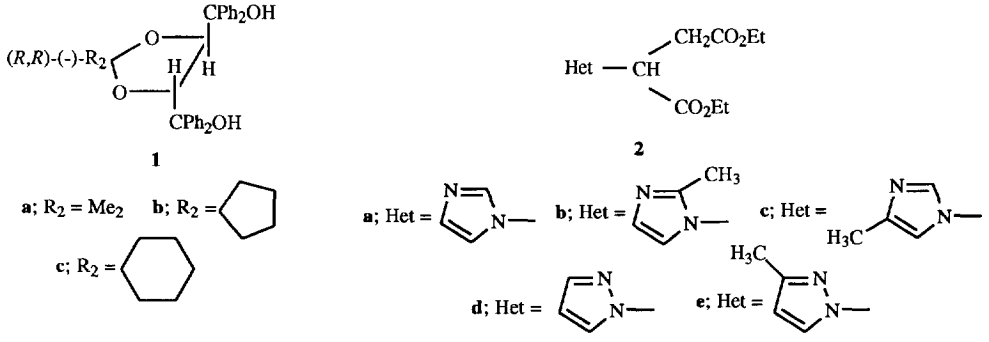
Abstract: Some racemic 2-imidazol-1-yl and 2-pyrazol-1-ylsuccinic esters, prepared by nucleophilic addition of the corresponding azole to fumaric esters, have been resolved. The enantioselective inclusion methodology has been applied using compounds derived from tartaric acid as chiral hosts.

We have recently proposed diethyl 2-imidazol-1-ylsuccinate as an extrinsic probe for the measurement of the intracellular pH in red cells.[1,2] It was regioselectively hydrolyzed to its half-ester in the biological medium,[1,2] and by a mild neutral hydrolysis with water.[3] The synthesis of the azol-1-ylsuccinic esters can be easily performed by nucleophilic addition of the corresponding azole to fumaric or maleic esters.[3] As had been previously found for the pyrazole derivative,[4] the reaction was non-stereoselective and the racemic diester was obtained in all cases. Due to the capability of the half-esters to behave as metal ligands useful in organic and bioorganic applications, we decided to carry out the enantiomeric resolution of the precursor diesters. Neutral hydrolysis of the resolved 2-imidazol-1-ylsuccinic esters would allow the preparation of the enantiomerically pure 3-(alkoxycarbonyl)-2-imidazol-1-ylpropionic acids, useful chiral ligands in organometallic chemistry.



Recently, some of us described that efficient resolution can be achieved by enantioselective inclusion complex formation with chiral host compounds of type **1**.[5] These compounds can interact through hydrogen-bonding with a polar guest to induce an effective host-guest inclusion complex.[6] In this work we have resolved a series of 2-azol-1-ylsuccinic esters **2a-e**, using compounds **1a-c** as chiral hosts.



In this methodology two different procedures can be used, either the recrystallization method or the suspension in water method (see experimental part). Tables 1 and 2 summarize the results obtained in the resolution of compounds **2a-e** by both methods.

Table 1. Results of resolutions by the recrystallization method.

Host	Guest	Yield (%)	Optical Purity (% e.e)	$[\alpha]_D$ [c]
1a	**2a**	26	90[a]	+3.4
1b	**2a**	98	11[a]	+0.3
1c	**2a**	69	53[a]	+1.7
1b	**2b**	98	26[b]	+16.3
1c	**2b**	100	15[b]	+11.0
1a	**2c**	46	83[a]	-13.2
1b	**2c**	93	41[a]	-3.1
1c	**2c**	80	31[a]	-3.0
1b	**2d**	85	97[a]	+48.6
1c	**2d**	93	98[a]	+47.6
1b	**2e**	93	51[a]	+42.6
1c	**2e**	95	36[a]	+29.6

[a,b]Determined by HPLC using a column containing optically active solid phase: Chiralpak AS and Chiralcel OJ, respectively; [c]Measured in EtOH at the concentration of c 0.5.

Table 2. Results of resolutions by the water suspension method.

Host	Guest	Yield (%)	Optical Purity (% e.e)	$[\alpha]_D$ [c]
1a	**2a**	69	52[a]	+1.8
1b	**2a**	92	15[a]	+0.9
1c	**2a**	72	92[a]	+3.1
1b	**2b**	96	41[b]	+19.8
1c	**2b**	98	26[b]	+15.9
1a	**2c**	100	100[a]	-16.6
1b	**2c**	94	78[a]	-7.8
1c	**2c**	88	53[a]	-5.6
1b	**2d**	94	73[a]	+38.7
1c	**2d**	75	91[a]	+45.6
1b	**2e**	92	16[a]	+13.1
1c	**2e**	97	58[a]	+49.0

[a,b]Determined by HPLC using a column containing optically active solid phase: Chiralpak AS and Chiralcel OJ, respectively; [c]Measured in EtOH at the concentration of c 0.5.

A comparison of the results shown in both tables indicates that imidazole derivatives were better resolved by the water suspension method using either **1a** or **1c** as chiral host compounds. However, pyrazole derivatives, especially **2d**, seemed to be less sensitive to host complexation, and similar resolutions were achieved with both host compounds **1b** and **1c**.

Experimental Section

Melting points were obtained on a Yanako micro melting point apparatus and are uncorrected. Optical rotations were measured in a 1-dm cell of 1 mL capacity using a Jasco Dip-140 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Jeol PMX-60SI NMR spectrometer. Elemental analyses were carried out with a Perkin Elmer L-4000 apparatus. Column chromatography was performed through silica gel Merck 60 (70-230 mesh). Chiral HPLC was performed on a Hitachi L-6000 pump equipped with a Hitachi L-4000 UV detector. The optically pure diol host compounds **1a-c**,[7-9] (±)-diethyl 2-imidazol-1-ylsuccinate **2a**,[1,2] and (±)-diethyl 2-pyrazol-1-ylsuccinate **2d**[3,4] were prepared according to literature procedures.

Diethyl (±)-2-(2-methylimidazol-1-yl)succinate (2b). A solution of diethyl fumarate (7 g, 40.7 mmol) and 2-methylimidazol (6.57 g, 81.3 mmol) in toluene (50 mL) was heated under reflux for 24 h. The residue left after evaporation of the solvent was chromatographed on silica gel using CH_2Cl_2 as eluent to give **2b** (8.9 g) as an oil which upon Kugelrohr distillation o.t.$_2$ 220 °C gave pure **2b** (8.72 g, 85%). IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 6 H, two $CH_2C\underline{H}_3$), 2.43 (s, 3 H, CH_3), 2.62-3.56 (m, 2 H, CH_2), 4.12 and 4.23 (each q, J = 7 Hz, 2 H, $C\underline{H}_2CH_3$), 5.20 (t, J = 7 Hz, 1 H, CH), 6.86- 7.02 (m, 2 H, arom.).

Diethyl (±)-2-(4-methylimidazol-1-yl)succinate (2c). A solution of diethyl fumarate (7 g, 40.7 mmol) and 4-methylimidazol (6.57 g, 81.3 mmol) in toluene (50 mL) was heated under reflux for 24 h. The residue left after evaporation of the solvent was chromatographed on silica gel using CH_2Cl_2 as eluent to give **2c** (5.03 g) as an oil which upon Kugelrohr distillation o.t.$_2$ 220 °C gave pure **2c** (4.19 g, 41%). IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 and 1.21 (each t, J = 7 Hz, 6 H, two $CH_2C\underline{H}_3$), 2.21 (s, 3 H, CH_3), 3.05 (t, J = 7 Hz, 2 H, CH_2), 4.11 and 4.23 (each q, J = 7 Hz, 2 H, $C\underline{H}_2CH_3$), 5.12 (t, J = 7 Hz, 1 H, CH), 6.68 (br s, 1 H, H-5), 7.42 (br s, 1H, H-2).

Diethyl (±)-2-(3-methylpyrazol-1-yl)succinate (2e). A solution of diethyl fumarate (10 g, 58.1 mmol) and 3-methylpyrazol (7.15 g, 87.1 mmol) in toluene (50 mL) was heated under reflux for 24 h. The residue left after evaporation of the solvent was chromatographed on silica gel using hexane-ethyl acetate as eluent to give **2e** (12.25 g) as an oil which upon Kugelrohr distillation o.t.$_2$ 220 °C gave pure **2e** (12.15 g, 82%). IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 6 H, two $CH_2C\underline{H}_3$), 2.28 (s, 3 H, CH_3), 3.11-3.54 (m, 2 H, CH_2), 4.15 and 4.30 (each q, J = 7 Hz, 2 H, $C\underline{H}_2CH_3$), 5.34 (t, J = 7 Hz, 1 H, CH), 6.10 (d, J = 2 Hz, 1 H, H-4), 7.48 (d, J = 2 Hz, 1 H, H-5).

General procedure of resolution by the recrystallization method. For example, a solution of (±)-**2a** (0.5 g, 2.09 mmol) and **1a** (0.49 g, 1.04 mmol) in toluene (1 mL)-hexane (2 mL) was kept at room temperature for 24 h to give a 1:1 inclusion complex of **1a**:(+)-**2a** (0.19 g, 26%) as colorless needels: mp 114-116 °C; $[\alpha]_D^{20}$ -33.8 (c 0.07, $CHCl_3$); IR (nujol) 3175, 1745, 1720 cm^{-1}; Anal. Calcd. for $C_{42}H_{46}N_2O_8$: C, 77.37; H, 6.56; N, 3.96. Found: C, 77.12; H, 6.62; N, 4.05.

Column chromatography of the inclusion complex on silica gel using CH_2Cl_2:EtOH (97:3) as eluent gave (+)-**2a** of 90% ee as an oil (0.06 g, 26%). The enantiomeric excess was determined by HPLC on the chiral solid phase Chiralpak AS. **2b-e** were resolved by the same procedure, the enantiomeric excess and

chemical yields are shown in Table 1. Physical and analytical data of inclusion complex crystals of **1a-c** with **2b-e** are indicated below.

Complex 1b:2b (1:1): mp 111-112 °C; $[\alpha]_D^{20}$ -19.1 (c 0.49, $CHCl_3$); IR (Nujol) 3170, 1740, 1725 cm^{-1}; Anal. Calcd. for $C_{45}H_{50}N_2O_8$: C, 72.37; H, 6.76; N, 3.75. Found: C, 72.36; H, 6.73; N, 3.76.

Complex 1c:2b (1:1): mp 115-116 °C; $[\alpha]_D^{20}$ -42.0 (c 0.44, $CHCl_3$); IR (Nujol) 3170, 1740, 1720 cm^{-1}; Anal. Calcd. for $C_{46}H_{52}N_2O_8$: C, 72.60; H, 6.89; N, 3.68. Found: C, 72.69; H, 6.80; N, 3.68.

Complex 1b:2c (1:1): mp 95-103 °C; $[\alpha]_D^{20}$ -30.4 (c 0.46, $CHCl_3$); IR (Nujol) 3190, 1740, 1720 cm^{-1}; Anal. Calcd. for $C_{45}H_{50}N_2O_8$: C, 72.37; H, 6.76; N, 3.75. Found: C, 72.33; H, 6.89; N, 3.97.

Complex 1c:2c (1:1): mp 119-134 °C; $[\alpha]_D^{20}$ -50.0 (c 0.41, $CHCl_3$); IR (Nujol) 3260, 1730, 1720 cm^{-1}; Anal. Calcd. for $C_{46}H_{52}N_2O_8$: C, 72.60; H, 6.89; N, 3.68. Found: C, 72.68; H, 6.90; N, 3.42.

Complex 1b:2d (2:1): mp (not clear); $[\alpha]_D^{20}$ -22.8 (c 0.45, $CHCl_3$); IR (Nujol) 3480, 3190, 1745, 1710 cm^{-1}; Anal. Calcd. for $C_{77}H_{80}N_2O_{12}$: C, 75.47; H, 6.58; N, 2.29. Found: C, 75.66; H, 6.43; N, 2.23.

Complex 1c:2d (2:1): mp (not clear); $[\alpha]_D^{20}$ -53.4 (c 0.53, $CHCl_3$); IR (Nujol) 3490, 3310, 1745, 1710 cm^{-1}; Anal. Calcd. for $C_{79}H_{84}N_2O_{12}$: C, 75.70; H, 6.75; N, 2.24. Found: C, 75.92; H, 6.99; N, 2.22.

Complex 1b:2e (2:1): mp (not clear); $[\alpha]_D^{20}$ -23.7 (c 0.41, $CHCl_3$); IR (Nujol) 3450, 3280, 1740, 1705 cm^{-1}; Anal. Calcd. for $C_{78}H_{82}N_2O_{12}$: C, 75.58; H, 6.67; N, 2.26. Found: C, 75.49; H, 6.96; N, 2.24.

Complex 1c:2e (2:1): mp 103-104 °C; $[\alpha]_D^{20}$ -51.1 (c 0.37, $CHCl_3$); IR (Nujol) 3460, 3300, 1740, 1705 cm^{-1}; Anal. Calcd. for $C_{80}H_{86}N_2O_{12}$: C, 77.02; H, 6.95; N, 2.25. Found: C, 76.46; H, 6.83; N, 1.99.

General procedure of resolution by the water suspension method. For example, when a suspension of finelly powdered **1a** (0.25 g, 0.54 mmol) and (±)-**2a** (0.26g, 1.08 mmol) in water (2.5 mL), containing cetyltrimetylammonium bromide as a surfactant, was stirred at room temperature for 24 h, the inclusion complex of **1a** and (+)-**2a** (0.34 g) was obtained as a colourless powder. Column chromatography of the powder on silica gel using CH_2Cl_2/EtOH (97:3) as eluent gave pure (+)-2a of 52% ee (0.09 g, 69%) as an oil. The optical purity was determined by HPLC on the solid phase Chiralpak AS. **2b-e** were resolved by the same procedure, the enantiomeric excess and chemical yields are shown in Table 2.

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