Synthesis and Characterization of New 1,1'-Diester, Diketone, and Dinitrile Derivatives of 2,2'-Biimidazole

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Substituted 1,1'-diester, diketone and dinitrile derivatives are prepared from 2,2'-biimidazole. The reactions involved include: Michael addition with halogenated olefins; nucleophilic substitution with ketones, nitriles, and esters; and condensation with amines.

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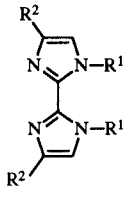
Compounds containing 2,2'-biimidazole have long been investigated for their metal binding ability. Complexes with Cu(II) [1,2], Ni(II) [1,2], Fe(II) [1,2], Co(II) [1,2], Rh(I) [3,4], Pd(II) [5], Ru(II) [6], Mo(V,VI) [7] and U(VI) [7] have been prepared and are generally well characterized. In addition, derivatives of 2,2'-biimidazole have been studied on the basis of their biological activity [8-11]. In recent years, interest in heterocyclic aromatic polymers and macrocycles that show potential as electrical conductors [12], catalysts [13-15], enzymatic active-site models [16,17], and for selective metal ion binding [18-20] has prompted investigations into the synthesis, polymerization, and cyclization [21,22] of various monomers containing the 2,2'-biimidazole moiety. By far, the monomer having received the most attention is 1,1'-di(hydroxyethyl)-2,2'-biimidazole [10]. This diol has been used in the synthesis of polyurethanes [23], polyesters [24], and polycarbonates [25]. In addition, vinyl polymers containing pendent and backbone 2,2'-biimidazole units have been studied [26].

We now wish to present the synthesis of several new 1,1'-diester, diketone and dinitrile derivatives of 2,2'-biimidazole (Scheme I). The synthesis and metal binding properties of the macrocycles and polymers derived from these new compounds are currently being investigated.

Scheme I



1	$R^1 = CH_2CN$, $R^2 = H$
2	$R^1 = CH_2COOCH_3$, $R^2 = H$
3a	$R^1 = CH_2CONH(CH_2)_2NH_2$, $R^2 = H$
3b	$R^1 = CH_2CONH(CH_2)_2NH(CH_2)_2$, $R^2 = H$
4	$R^1 = (CH_2)_2COCH_3$, $R^2 = H$
5	$R^1 = CH_2COPh$, $R^2 = NO_2$
6	$R^1 = CH_2COPh$, $R^2 = H$
7	$R^1 = CH_2OCCH_3$, $R^2 = H$

EXPERIMENTAL

Melting points were determined using an Electrothermal Melting Point Apparatus and are uncorrected. The ^1H nmr spectra were obtained using a Jeol FX100 (100 MHz) spectrometer, with tetramethylsilane or sodium trimethylsilylpropionate as reference. Infrared spectra were obtained from a Perkin Elmer 1750 Infrared Fourier Transform Spectrometer as potassium bromide pellets. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxsville, TN, or Quantitative Technologies Inc., Whitehouse, NJ.

2,2'-Biimidazole [27] and 4,4'-dinitro-2,2'-biimidazole [11] were prepared according to published procedures. All other reagents were obtained from Aldrich Chemical Co., and used as received.

1,1'-Di(cyanomethyl)-2,2'-biimidazole (**1**).

To 13.4 g (0.10 mole) of 2,2'-biimidazole in 900 ml of *N,N*-dimethylformamide (DMF), heated to approximately 50°, was added 26 ml of 6.0 *N* aqueous sodium hydroxide. A dark green solution resulted within 30 minutes. To this mixture, 7 ml (0.05 mole) of chloroacetonitrile in 50 ml of DMF was added in 3 ml aliquots over a period of 15 minutes. Ten minutes later, an additional 17 ml of 6.0 *N* aqueous sodium hydroxide was added, followed 10 minutes later by 7 ml (0.05 mole) of chloroacetonitrile, in 50 ml of DMF, in 3 ml aliquots over a period of 15 minutes. After 4 hours, 5 ml of 1.0 *N* hydrochloric acid was added and heating discontinued. Vacuum distillation was used to remove DMF leaving approximately 5 ml of slurry. The product was extracted with 600 ml of refluxing acetone. The red-orange solution was rotoevaporated to approximately 50 ml after which light tan crystals formed immediately upon cooling. The slurry was transferred into a beaker and the solvent allowed to evaporate to 15 ml. The remaining liquid was carefully decanted, and the crystals were washed with two 5 ml aliquots of methanol, then recrystallized twice from absolute ethanol to yield white needles, 9.30 g (44%), mp 215-216°; ir: ν 3140, 3004 (Ar-H), 2253 (CN) cm^{-1}; ^1H nmr (d_6-acetone): δ 5.9 (s, 4H, CH_2), 7.2 (s, 2H, H_5, $H_{5'}$), 7.5 (s, 2H, H_4, $H_{4'}$).

Anal. Calcd. for $C_{10}H_8N_6$: C, 56.60; H, 3.80; N, 39.60. Found: C, 56.15; H, 3.98; N, 39.41.

1,1'-Di(methylacetato)-2,2'-biimidazole (**2**).

To 10.72 g (0.08 mole) of 2,2'-biimidazole in 720 ml of DMF at 50° was added 15 ml of 6.0 *N* sodium hydroxide. One equivalent of methylchloroacetate (7.2 ml, 0.04 mole) was then added to the resulting dark green solution. After 30 minutes, 13.6 ml of 6 *N* sodium hydroxide was added followed 20 minutes later by a second equivalent of methylchloroacetate (7.2 ml, 0.04 ml). The reaction was stirred for 2 hours after which 2.8 ml of 3 *N* hydrochloric acid was added and heating discontinued. *N,N*-Dimethylformamide was removed using vacuum distillation. The product was extracted with 600 ml of refluxing acetone. The red solution was rotoevaporated to dryness, cooled, washed with a small amount of methanol, and then recrystallized from 300 ml of methanol to yield lusterous pale yellow needles, 1.75 g (17%), mp 206°; ir: ν 3111, 2955 (Ar-H), 1764, 1225 (COO) cm^{-1}; ^1H nmr (d_7-DMF): δ 3.7 (s, 6H, CH_3), 5.5 (s, 4H, CH_2), 7.0 (d, 2H, H_5, $H_{5'}$), 7.3 (d, 2H, H_4, $H_{4'}$).

Anal. Calcd. for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13; O, 23.00. Found: C, 51.42; H, 5.13; N, 20.16; O, 23.29.

General Procedure for the Preparation of Substituted 1,1'Diacetamides of 2,2'-Biimidazole **3**.

To 0.21 g (0.75 mmole) of 1,1'-di(methylacetato)-2,2'-biimidazole **2** was added 3 ml of either diethylene triamine or ethylene diamine and the mixture was gently warmed to 30° for 12 hours with stirring. After 1 hour, the mixture became a clear, pale yellow solution. The solution was stirred an additional 12 hours at room temperature, and a white precipitate formed. The diacetamide was diluted, filtered, and washed with 50 ml of tetrahydrofuran. The total reaction time was 24 hours. In this manner the following compounds were prepared.

1,1'-Di(aminoethyl acetamido)-2,2'-biimidazole (**3a**).

The yield was 0.18 g (75%), mp 195-200° dec (from ethanol); ir: ν 3345, 2955 (NH), 1678, 1595 (CON) cm^{-1}; ^1H nmr (deuterium oxide): δ 2.5-2.8 (t, 4H, CH_2), 3.1-3.4 (t, 4H, CH_2), 5.0 (s, 4H, CH_2), 7.2 (s, 2H, H_5, $H_{5'}$), 7.3 (s, 2H, H_4, $H_{4'}$).

Anal. Calcd. for $C_{14}H_{22}N_8O_2$: C, 50.28; H, 6.64; N, 33.51. Found: C, 50.59; H, 6.41; N, 33.72.

1,1'-Di(aminoethylaminoethyl acetamido)-2,2'-biimidazole (**3b**).

The yield was 0.132 g (42%), mp 128-129° (from 1,4-dioxane); ir: ν 3300, 3150 (NH), 1669, 1566 (CON) cm^{-1}; ^1H nmr (d_4-methanol): δ 2.5-2.7 (m, 16H, CH_2), 5.1 (s, 4H, CH_2), 7.1 (d, 2H, H_5, $H_{5'}$), 7.3 (d, 2H, H_4, $H_{4'}$).

Anal. Calcd. for $C_{18}H_{32}N_{10}O_2$: C, 51.40; H, 7.68; N, 33.31. Found: C, 51.53; H, 7.44; N, 33.09.

1,1'-Di(2-butanone)-2,2'-biimidazole (**4**).

A suspension of 2.68 g (0.02 mole) of 2,2'-biimidazole in 200 ml of DMF was stirred at 40°. A catalytic amount of sodium hydroxide (0.002 mole) was then added, and the solution was stirred for 20-30 minutes. Over a period of 2-3 hours, 2.8 g (0.04 mole) of methyl vinyl ketone in 100 ml of DMF was added dropwise. Heating was then discontinued, and the solution was allowed to cool to room temperature. The solution was then neutralized with aqueous hydrochloric acid. The mixture was filtered, and DMF was removed by vacuum distillation. The product was then recrystallized from 1,4-dioxane, 4.6 g (84%), mp 75-77°; ir: ν 3121 (Ar-H), 1708, 1163 (CO) cm^{-1}; ^1H nmr (d_7-DMF): δ 2.2 (s, 6H, CH_3), 3.0-3.3 (t, 4H, α-proton), 4.6-4.9 (t, 4H, β-proton), 7.0-7.1 (d, 2H, H_5, $H_{5'}$), 7.4-7.5 (d, 2H, H_4, $H_{4'}$).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 60.85; H, 6.38; N, 20.47.

1,1'-Di(benzoylmethyl)-4,4'-dinitro-2,2'-biimidazole (**5**).

A solution of 0.45 g (0.002 mole) of 4,4'-dinitro-2,2'-biimidazole in 40 ml of DMF was stirred at 80°. Slightly more (<5%) than one equivalent of sodium hydroxide (0.35 ml of 6 *N*) was added to the solution. The solution was heated at reflux for 15 minutes, after which, one equivalent (0.40 g, 0.002 mole) of bromoacetophenone, dissolved in 5 ml of DMF, was added over a period of 15 minutes. The solution was refluxed for 20 minutes, after which the second equivalent of 6 *N* aqueous sodium hydroxide (0.35 ml) was added. Following a 15 minute period of refluxing, the second equivalent of bromoacetophenone (0.40 g, 0.002 mole) was added. The mixture was refluxed for an additional 2-3 hours. Heating was discontinued and the excess base was then neutralized with aqueous hydrochloric acid. The solution was cooled slowly to room temperature, filtered, and DMF removed by vacuum distillation. The product was then recrystallized from acetone, 0.22 g (28%), mp >250° dec; ir: ν 3139 (Ar-H), 1690, 1298 (CO), 1542 (NO_2), 755 (Ar-R) cm^{-1}; ^1H nmr (d_7-DMF): δ 6.5 (s, 4H, CH_2), 7.6-7.8 (m, 6H, Ph-H_2, H_3, H_4), 8.1-8.3 (d, 4H, Ph-H_1, H_5), 8.7 (s, 2H, H_5, $H_{5'}$).

Anal. Calcd. for $C_{22}H_{16}N_6O_6$: C, 57.39; H, 3.50; N, 18.25. Found: C, 57.07; H, 3.38; N, 18.08.

1,1'-Di(benzoylmethyl)-2,2'-biimidazole (**6**).

A suspension of 1.00 g (0.007 mole) of 2,2'-biimidazole in 100 ml of DMF was stirred at 50°. Slightly more than (<5%) one equivalent of sodium hydroxide (1.87 ml, 6 *N*) was added to the solution. Once the solution became dark green, one equivalent (1.484 g, 0.007 mole) of bromoacetophenone was added. This reaction mixture was stirred, for 30-40 minutes, resulting in precipitate formation. After addition of the second equivalent of sodium hydroxide (1.85 ml, 6 *N*) the initial precipitate was resolubilized. The reaction mixture was allowed to stir another 30 minutes, after which the second equivalent of bromoacetophenone (1.484 g, 0.007 mole) was introduced. The reaction was refluxed for 1.5-2.0 hours. The heat was then discontinued, and the solution slowly cooled to room temperature. The solution was then neutralized with aqueous hydrochloric acid. The product, an off-white crystalline solid, was filtered from the reaction mixture, washed thoroughly with 100 ml of water, and then dried *in vacuo,* 1.30 g (47%), mp >230° dec; ir: ν 3137 (Ar-H), 1695, 1290 (CO), 764 (Ar-R) cm^{-1}; ^1H nmr (deuterium chloride, 18 wt% solution in deuterium oxide): δ 6.9 (s, 4H, CH_2), 7.5-7.6 (m, 6H, Ph-H_2, H_3, H_4), 7.7-7.8 (d, 4H, Ph-H_1, H_5), 8.04 (s, 2H, H_5, $H_{5'}$), 8.08 (s, 2H, H_4, $H_{4'}$).

Anal. Calcd. for $C_{22}H_18N_4O_2$: C, 71.33; H, 4.90; N, 15.13. Found: C, 71.03; H, 4.81; N, 15.31.

1,1'-Di(2-propanone)-2,2'-biimidazole (**7**).

A suspension of 2.5 g of 2,2'-biimidazole (0.0186 mole) in 200 ml of DMF was stirred at 80°. Slightly more than (<5%) one equivalent of sodium hydroxide (3.25 ml, 6 *N*) was added to the solution. The solution was stirred for 15-20 minutes, after which, 1.56 ml (0.0186 mole) of 95% chloroacetone was added dropwise. The solution was stirred for an additional 15 minutes and then 3.1 ml of sodium hydroxide (6 *N*) was added. This was stirred for 15 minutes, after which the second equivalent of 95% chloroacetone (1.56 ml, 0.0186 mole) was added dropwise. The reaction proceeded for 2.0-2.5 hours. Heating was discontinued and excess base was neutralized with aqueous hydrochloric acid. The solution was filtered, and DMF removed by vacuum distillation. The product was then recrystallized from acetone, 1.58 g (34%), mp 180° dec; ir: ν 3129 (Ar-H), 1729, 1180 (CO) cm^{-1}; ^1H nmr (d_7-DMF): δ 2.2 (s, 6H, CH_3), 5.5 (s, 4H, CH_2), 7.0 (s, 2H, H_5, $H_{5'}$), 7.3 (s, 2H, H_4, $H_{4'}$).

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.31; H, 5.73; N, 22.77.

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