SYNTHESIS OF 1*H*-INDOLYL-2-BENZIMIDAZOLES AND 1*H*-INDOLYL-2-BENZOTHIAZOLES

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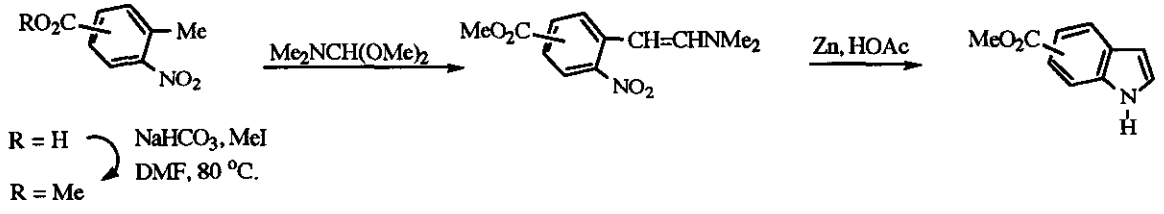
Abstract - A convenient synthesis of regioisomeric 1*H*-indolyl-2-benzimidazoles and -2-benzothiazoles by the direct conversion of indole-esters with the *in situ* generated organoaluminum reagents trimethylaluminum-1,2-diaminobenzene or trimethylaluminum-2-aminothiophenol is reported.

Recent interest has focused on biaryl indoles as anticancer agents, antiviral agents and inhibitors of cell signaling and signal transduction pathways.[1] As part of our research directed toward the study of biologically interesting indole molecules we required a synthesis of regioisomeric 1*H*-indolyl-2-benzimidazoles and 1*H*-indolyl-2-benzothiazoles. A number of conventional methods for benzimidazole and benzothiazole formation have been reported.[2] Many of these approaches were precluded for the synthesis of these compounds due to the reactivity of the indole nucleus. It is well documented the indole C-3 position is susceptible to electrophilic reactions, acylations *via* acid chlorides and acid catalyzed carbonyl condensations.[3] The use of indolealdehydes is an ineffective route for benzimidazoles with the indole nucleus.[4] Attempts to prepare the 3-indolyl-2-benzimidazole isomer from indole-3-carboxaldehyde gave the desired biaryl as a minor product in low yield (22% yield). The disubstituted benzimidazole, 1-(3-indolylmethyl)-2-(3-indolyl)benzimidazole, was the major product (65%) synthesized.[4] This paper describes a convenient method of synthesis and the characterization of new 1*H*-indolyl-2-benzimidazoles and 1*H*-indolyl-2-benzothiazoles starting with indoleesters.

In selected cases, esters can react directly to give benzimidazoles and benzothiazoles although drastic reaction conditions and temperatures often limit the usefulness of these procedures.[2] The synthesis of amides from esters using dimethylaluminum amides[5] has shown wide synthetic application under mild reaction conditions. The indoleesters substituted in the aryl portion (indole positions 5 and 6) were prepared using Batcho-Leimgruber methodology (Scheme 1) starting with the appropriate nitro-methyl-benzoic acids.[6]

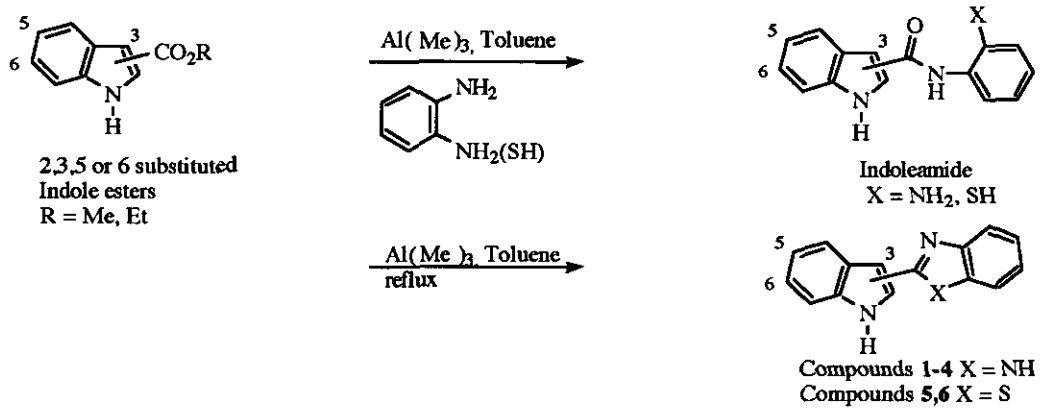
Scheme 1



The indoleesters were converted to 1*H*-indolyl-2-benzimidazoles and 1*H*-indolyl-2-benzothiazoles in one pot by treatment with the appropriate organoaluminum reagent (Scheme 2). The organoaluminum reagent was generated *in situ* from 1,2-diaminobenzene (DAB) and trimethylaluminum (TMA) in toluene at 0 °C, followed by warming to 15-20 °C to produce a homogeneous solution with the liberation of methane. The best conditions were found using an excess of TMA. Using 1 or 2 equivalents of TMA:DAB yielded primarily indoleamide (Scheme 2). The exact nature of the organoaluminum reagent is uncertain. Trimethylaluminum reacts with ammonia or primary and secondary amines in a 1:1 molar ratio at ambient temperatures to give dimethylaluminum amides.[8] A monomeric species is less likely to exist in solution in the presence of excess $AlMe_3$. Treatment of ethyl indole-2-carboxylate (1 equivalent) with $AlMe_3$:1,2-diaminobenzene (5:1.5 equivalents) gave 50% benzimidazole (**1**) with traces of indoleamide (Scheme 2). Using these reaction conditions (indole ester: $AlMe_3$: DAB; 1: 5: 1.5) methyl indole-3-carboxylate was converted to benzimidazole (**2**) in 55% yield. Isomers substituted in the aromatic positions of the indole nucleus (indole 5 and 6 positions) were converted to benzimidazoles in more favorable yields compared to the 2- and 3-substituted indoles. Ethyl indole-5-carboxylate gave 2-(5-indolyl)benzimidazole (**3**) in 66% yield and ethyl indole-6-carboxylate gave 2-(6-indolyl)benzimidazole (**4**) in 72% yield. The reagent produced from 2-aminothiophenol-

trimethylaluminum was similarly generated and used to prepare the corresponding benzothiazole analogs. Indole-2- and -5-carboxylates readily gave 2-(2-indolyl)benzothiazole (53%) (**5**) and 2-(5-indolyl)benzothiazole (60%) (**6**) respectively.

Scheme 2



EXPERIMENTAL.

Melting points were determined on a Electrothermal Digital Melting Point Apparatus and are uncorrected. Proton and carbon nmr spectra were recorded on a QE-300 spectrometer with tetramethylsilane as an internal standard. Mass spectra (ms) were carried out on a VG Analytical ZAB 2-SE high field mass spectrometer using a cesium ion gun to generate ions. Infrared spectra (ir) were obtained with a Perkin-Elmer 1320 spectrophotometer. Elemental analyses were performed by Quantitative Technologies, Whitehouse, NJ, USA. Spectral data was consistent with the assigned structures. Column chromatography was performed on silica gel 60 (230-400 mesh).

Typical Procedure: A dry 100 ml 3-neck round-bottom flask, equipped with a magnetic stirrer, reflux condenser, and nitrogen adapter was charged with anhydrous toluene (50 ml) and trimethylaluminum (26.9 mmol of 2.0 M solution in toluene). The solution was cooled to 0 °C, then 1,2-diaminobenzene (865 mg, 8.0 mmol) was added in small portions with stirring. The solution was stirred 30 min at 0 °C, then at 15-20 °C until evolution of methane ceased (*ca.* 0.5-1 h). To the resulting pink solution was added the indole ester (5.3 mmol) in one portion at ambient temperature, then the mixture was maintained at reflux 12-14 h. After cooling the mixture on an ice bath, water (10 ml) was cautiously added, followed

by MeOH (100 ml). The solid precipitate was removed by filtration and washed with MeOH (25 ml). The combined organic solutions were concentrated under reduced pressure. Cold 2 N HCl (5 ml) was added to the residue and the product triturated to a white solid and collected by filtration. The product, as the HCl salt or free base (generated from $CHCl_3$/ 2N Na_2CO_3 extraction) was purified by recrystallization or by column chromatography (silica gel; EtOAc:hexanes; 2:1, or CH_2Cl_2:MeOH:NH_4OH; 95:5: 0.5).

2-(1*H*-Indol-2-yl)-1*H*-benzimidazole Hydrochloride (**1**): white powder (MeOH-ether) 50%; mp 328-329 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 7.18 (t, 1H, J = 7.8 Hz), 7.35 (t, 1H, J = 7.8 Hz), 7.48-7.58 (m, 3H); 7.59 (d, 1H, J = 8.2 Hz), 7.66 (s, 1H), 7.78-7.90 (m, 2 H), 12.40 (s, 1H); ^{13}C nmr (DMSO-d_6, 300 MHz) δ 107.7, 112.8, 114.3, 114.4, 121.4, 122.4, 123.0, 125.6, 125.7, 127.7, 138.3, 144.0; ir (KBr) 3320, 3180, 1630, 1590, 1450, 1420, 1340, 1230, 1110, 820, 740 (cm^{-1}); ms (FAB) m/z = 234 (m+1)$^+$; Anal. Calcd for $C_{15}H_{11}N_3 \cdot HCl \cdot 0.75\,H_2O$: C, 63.61; H, 4.80; N, 14.84. Found: C, 63.67; H, 4.74; N, 14.76.

2-(1*H*-Indol-3-yl)-1*H*-benzimidazole Hydrochloride (**2**): white powder (MeOH-ether) 55%; mp 332-333 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 7.38 (m, 2H), 7.55 (m, 2H), 7.64 (m, 1H), 7.80 (m, 2H), 8.34 (m, 1H), 8.60 (s, 1H), 12.52 (s, 1H); ^{13}C nmr (DMSO-d_6, 300 MHz) δ 99.7, 113.6, 113.8, 120.1, 122.4, 123.8, 124.0, 125.5, 132.1, 132.7, 137.2, 146.6; ir (KBr) 3340, 3120, 1620, 1585, 1440, 1420, 1370, 1320, 1175, 1140, 1250, 1190, 1170 820, 740 (cm^{-1}); ms (FAB) m/z = 234 (m+1)$^+$; Anal. Calcd for $C_{15}H_{11}N_3 \cdot HCl \cdot H_2O$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.31; H, 4.90; N, 14.53.

2-(1*H*-Indol-5-yl)-1*H*-benzimidazole (**3**): white powder (MeOH-H_2O) 66%; mp 236-237 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 6.57 (s, 1H), 7.14-7.18 (m, 2H), 7.44 -7.55 (m, 3H), 7.60 (d, 1H, J = 7 Hz), 7.98 (d, 1H, J = 9 Hz), 8.38 (s, 1H), 11.35 (s, 1H), 12.71 (s, 1H); ^{13}C nmr (DMSO-d_6, 300 MHz) δ 102.4, 112.3, 119.2, 120.5, 121.7, 122.2, 127.2, 128.2, 135.6, 137.2, 144.5, 153.7; ir (KBr) 3380, 3140, 1600, 1530, 1440, 1390, 1350, 1260, 1090, 890, 800, 760, 740 (cm^{-1}); ms (FAB) m/z = 234 (m+1)$^+$; Anal. Calcd for $C_{15}H_{11}N_3 \cdot 0.1\,H_2O$: C, 76.64; H, 4.80; N, 17.88. Found: C, 76.54; H, 4.75; N, 17.76.

2-(1*H*-Indol-6-yl)-1*H*-benzimidazole (**4**): white powder (MeOH-Et_2O) 72%; mp 234-236 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 6.51 (d, 1H, J = 2.1 Hz), 7.14-7.18 (m, 2H), 7.45-7.51 (m, 2H), 7.60-7.70 (m, 2H), 7.84 (d, 1H, J = 7.8 Hz), 8.24 (s, 1H), 11.45 (s, 1H), 12.78 (s, 1H); ^{13}C nmr (DMSO-d_6, 300 MHz) δ 101.9, 110.2, 118.3, 120.9, 122.1. 123.5, 128.1, 129.3, 136.2, 140.5, 147.2, 153.8; ir (KBr) 3380 , 1610, 1550, 1440, 1270, 1110, 1000, 810, 760, 740 (cm^{-1}); ms (FAB) m/z = 234 (m+1)$^+$; Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 76.75; H, 4.59; N, 17.70.

2-(1*H*-Indol-2-yl)benzothiazole (**5**): tan powder (MeOH-H_2O) 53%; mp 185-186 °C; ^1H nmr (DMSO-d_6, 300 MHz) δ 7.10 (t, 1H, J = 7 Hz), 7.2-7.31 (m, 2H), 7.44-7.6 (m, 3H), 7.64 (d, 1H, J = 8.0 Hz), 8.06 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 8.0 Hz), 12.22 (s, 1H); ^{13}C nmr (DMSO-d_6, 300 MHz) δ 105.5, 112.7, 120.7, 121.7, 122.8, 122.9, 124.5, 125.9, 127.2, 128.2, 131.5, 134.6, 138.2, 153.8, 160.4; ir (KBr) 3360, 1530, 1410, 1330, 1300, 1210, 1140, 1010, 920, 790, 730, 670 (cm^{-1}); ms (FAB) m/z = 251 $(m+1)^+$; Anal. Calcd for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19. Found: C, 71.97; H, 4.05; N, 11.06.

2-(1*H*-Indol-5-yl)benzothiazole (**6**): tan powder (MeOH-H_2O) 60%; mp 178-179 °C; ^1H nmr (DMSO-d_6, 300 MHz) δ 6.62 (d, 1H, J = 3 Hz), 7.42 (t, 1H, J = 7.8 Hz), 7.48-7.57 (m, 3H), 7.86 (d, 1H, J = 7.9 Hz), 8.00 (d, 1H, J = 8.0 Hz), 8.10 (d, 1H, J = 7.9 Hz), 8.32 (s, 1H), 11.47 (s, 1H); ^{13}C nmr (DMSO-d_6, 300 MHz) δ 102.8, 112.7, 120.5, 120.9, 122.6, 122.7, 124.7, 125.3, 126.9, 127.8, 128.4, 134.7, 138.1, 154.3, 169.6; ir (KBr) 3320 (br), 1600, 1450, 1430, 1340, 1320, 1230, 1090, 890, 860, 750, 720 (cm^{-1}); ms (FAB) m/z = 251 $(m+1)^+$; Anal. Calcd for $C_{15}H_{10}N_2S \cdot 0.67\ H_2O$: C, 68.66; H, 4.36; N, 10.68. Found: C, 68.93; H, 4.08; N, 10.30.

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