relative peak heights could be used to monitor their interconversion.

Figure 1 shows plots of ln $[(K - x)/(x + 1)]$ vs. t for **3** at three different temperatures (x = [anti]/[syn]) starting from *syn*-**3**. (A similar plot was obtained for 100 °C by using 1-nonanol as solvent, suggesting that H bonds do not contribute to the barriers.) The slopes of these lines, equal to the negatives of the sums of the forward and reverse rate constants, indicate the rapidity with which equilibrium ($x = K$) is approached at the various temperatures. If $\Delta H - T\Delta S = 0$ for the conversion of one isomer to the other, we would expect $K = 3$ based on statistics. In fact, we measure $K = 4 \pm 0.5$, indicating $\Delta H - T\Delta S < 0.5$ kcal/mol. (We also cannot rule out slight differences in ϵ_{300} contributing to the deviation from $K = 3$.) From the slopes of the lines in Figure 1, we can calculate k_1 and k_{-1} directly, knowing K. A linear plot of log (k_{-1}/T) vs. $1000/T$ for the three equilibrations was used to calculate $\Delta G^{\ddagger} = 30$ kcal/mol at 373 K, $\Delta H^{\ddagger} = 23$ kcal/mol, $\Delta S^{\ddagger} = -17$ cal/deg·mol, and k_{-1} (298 K) $\sim$ 1/year. Molecular models of **1** and **2** indicate that their rotational barriers should be at least as high. The most nearly analogous values of $\Delta G^{\ddagger}$ reported in the literature, those of unsymmetrically substituted hexaphenylbenzenes[13] and bromophenyl-substiuted porphyrins,[14] are also approximately 30 kcal/mol. A related study of atropisomerism has also been performed on tetraarylporphyrins, whose geometries have been exploited in the construction of hemoprotein models.[15]

The generalizability of the Suzuki coupling will enable us to prepare derivatives of **1–3** by employing functionalized boronic acids in the coupling reactions. Alternatively, we can carry out direct reactions on **2** or **3**. Furthermore, these derivatives will be rigid not only with respect to conformational interconversion but also with respect to significant deviations from 90° aryl–aryl dihedral angles. Ultimately, our goal of synthesizing rigid tridentate binding units should be realized through analogues of the compounds just discussed.

Acknowledgment. We thank Drs. F. M. Houlihan and R. C. Helgeson for valuable discussion of organometallic coupling reactions and A. M. Mujsce for obtaining mass spectra.

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Indole *N*-Carbonyl Compounds: Preparation and Coupling of Indole-1-carboxylic Acid Anhydride

Dale L. Boger[1] and Mona Patel*

Department of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907

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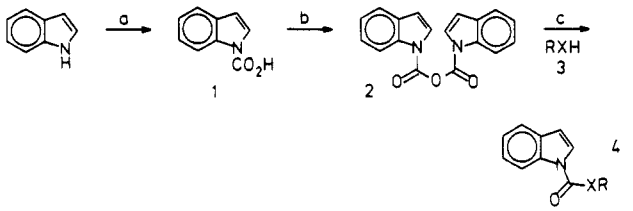
The preparation of indole *N*-carbonyl compounds requires the selective N-acylation of indole with accessible, available acylating agents,[2] and the well-recognized, competitive N-1 vs. C-3 acylation of indole has required the empirical determination of experimental conditions which favor predominant or exclusive N-acylation.[2,3] In addition, for systems for which no activated acylation reagent is available, the indole *N*-carbonyl compounds are currently inaccessible.

Scheme I[a]



[a] (a) 1.0 equiv of *n*-BuLi, ether, 0 °C, 0.5 h; CO_2, 88–94%; (b) 0.6 equiv of EDCI·HCl, CH_2Cl_2, 25 °C, 15 min, 86%; (c) Table I.

Herein, we detail the preparation and characterization of indole-1-carboxylic acid anhydride (**2**) and describe its use in selective, controlled coupling reactions with representative nucleophilic *and* nonnucleophilic alcohols, phenols, amines, anilines, thiols, indoles, and pyrroles (Scheme I). The use of indole-1-carboxylic acid anhydride (**2**) in selective, intermolecular coupling reactions provides the control for exclusive indole N-acylation *and* permits the preparation of indole *N*-carbonyl compounds for which no accessible, activated acylation reagent is available.

Indole-1-carboxylic acid (**1**),[4,5] free of indole-3-carboxylic acid, was prepared by treatment of *N*-lithioindole with carbon dioxide (indole, 1.0 equiv of *n*-BuLi, ether; CO_2, 2 h) and was found to proceed with exclusive N-carboxylation.[4] Treatment of indole-1-carboxylic acid (**1**) with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI·HCl, 0.6 equiv; methylene chloride, 25 °C, 15 min) provided indole-1-carboxylic acid anhydride (**2**, 86%), which was isolated as a stable, crystalline solid.

The results of a study of the intermolecular coupling of indole-1-carboxylic acid anhydride (**2**) with representative nucleophiles are detailed in Table I. Nucleophilic substrates including amines (Table I, entries 7, 10) and anilines (Table I, entry 6) were found to react rapidly with **2** to provide the mixed urea and urethanes cleanly. In the instances of the use of nonnucleophilic coupling substrates including alcohols (Table I, entry 8), phenols (Table I, entries 3–5), thiols (Table I, entry 9), or electron-deficient indoles and pyrroles (Table I, entries 1, 2, 11), the indole *N*-carbonyl compound formation was observed only with the use of the preformed sodium salts of the coupling substrates.

Although the stoichiometric use of the preformed, isolated reagent **2** proved to be the most dependable procedure for the formation of indole *N*-carbonyl compounds,

(1) National Institutes of Health research career development award recipient, 1983–1988 (CA 01134). Alfred P. Sloan research fellow, 1985–1989.
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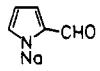
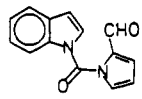
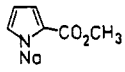
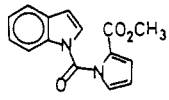
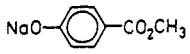
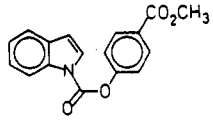
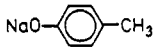
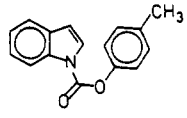
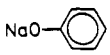
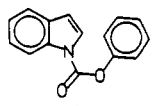
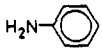
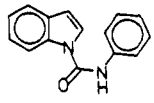
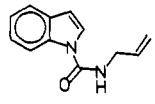
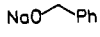
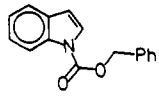
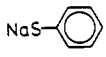
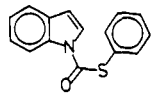
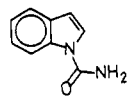
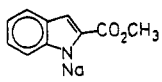
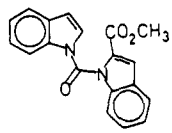
Table I. Coupling of Indole-1-carboxylic Acid Anhydride (2) in the Preparation of Indole *N*-Carbonyl Compounds

entry	coupling substrate 3	product[a]	% yield[b]	mp,[c] °C
1		 **4a**	89	oil
2		 **4b**	82	103–104
3		 **4c**	78	106–108
4		 **4d**	94	89–90
5		 **4e**	93	95–96
6		 **4f**	61	122–124
7		 **4g**	87[d] 91	oil
8		 **4h**	51	oil
9		 **4i**	68	oil
10	NH_4OH	 **4j**	79	171–172
11		 **4k**	72	oil

[a] All products exhibited the expected or previously reported ^1H NMR, IR, and EI/CIMS characteristics consistent with the assigned structure. All new compounds provided satisfactory HRMS determinations. [b] All yields are based on purified product (homogeneous) isolated by chromatography (SiO_2). All reactions were conducted by employing 1.2 equiv of **2** (THF, 25 °C, 15 min). [c] Melting point. [d] The reaction was conducted with the in situ generation of **2** by employing EDCI·HCl = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, see Experimental Section.

a procedure employing the use of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) for indole-1-carboxylic acid activation and anhydride formation (**1** → **2**) followed by in situ coupling with suitable substrates has proven to be a convenient, alternative procedure (Table I, entry 7). The workup, isolation, and purification of the sensitive indole *N*-carbonyl compounds was facilitated by the use of the water-soluble carbodiimide, EDCI·HCl, to promote the in situ anhydride formation.

Experimental Section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL-200 and chemical shifts are reported in parts per million relative to internal tetramethylsilane (0.00 ppm). Infrared spectra (IR) were recorded on a Perkin-Elmer 1800 Fourier transform spectrometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron impact mass spectra (EIMS) and chemical ionization mass spectra (CIMS) were recorded on a Finnegan 4000 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Kratos MS-50 spectrometer. CHN Analysis were performed by H. D. Lee at the Microanalytical Laboratories at Purdue University. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl, and benzene was distilled from calcium hydride. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. All extraction and chromatographic solvents; ethyl ether (Et_2O), ethyl acetate (EtOAc), and hexane, were distilled prior to use. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) was obtained from Aldrich Chemical Co. All reactions were performed under a positive atmosphere of nitrogen (N_2) or argon.

Indole-1-carboxylic Acid (1). A solution of *n*-BuLi (42.74 mmol, 18.58 mL of 2.3 M in hexanes) was added to a 0 °C solution of indole (5.0 g, 42.74 mmol) in dry ether. The resulting reaction mixture was allowed to stir at 0 °C (30 min) and poured onto a slurry of crushed dry ice (excess) in ether. The resulting mixture was stirred at 25 °C for 2 h and extracted with water. The aqueous layer was acidified to pH 1 with 5% aqueous hydrochloric acid and extracted with ether (5 × 100 mL). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford indole-1-carboxylic acid (**1**, 6.47 g, 6.88 g theoretical, 94%) as a white solid: mp 122–123 °C dec (benzene, white platelets) [lit.[4a] mp 107–108 °C (water), 128–129 °C[4b] dec (benzene)]; ^{1}H NMR ($CDCl_3$) δ 10.60 (br s, 1 H), 8.22 (d, 1 H, J = 8 Hz), 7.64 (d, 1 H, J = 3 Hz), 7.58 (d, 1 H, J = 8 Hz), 7.30 (m, 2 H), 6.66 (d, 1 H, J = 3 Hz); IR (KBr) ν_{max} 3154 (br), 2850, 2624, 1903, 1692, 1587, 1451, 1379, 1294, 1147, 1087, 903, 879, 766 cm^{-1}; EIMS, m/e (relative intensity) 161 (M^+, 32), 117 (base), 90 (50), 77 (2), 63 (14); CIMS (2-methylpropane), m/e (relative intensity) 162 ($M^+ + H$, 24), 118 ($M^+ + H - CO_2$, base); HRMS, m/e 161.0474 ($C_9H_7NO_2$ requires 161.0477).

Indole-1-carboxylic Acid Anhydride (2). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl, 7.45 mmol, 1.42 g, 0.6 equiv) was added to a 25 °C solution of indole-1-carboxylic acid (**1**, 12.42 mmol, 2.0 g) in dry CH_2Cl_2 (20 mL), and the resulting mixture was stirred at 25 °C for 15 min. The reaction mixture was diluted with water (10 mL) and extracted with ether (2 × 50 mL). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. Recrystallization (hexane/EtOAc, 4:1) afforded pure indole-1-carboxylic acid anhydride (**2**, 1.62 g, 1.88 g theoretical, 86%) as a white solid: mp 113–114 °C (hexane/EtOAc, 4:1; white needles); ^{1}H NMR ($CDCl_3$) δ 8.32 (br s, 2 H), 7.63 (m, 2 H), 7.59 (m, 2 H), 7.40 (m, 4 H), 6.74 (d, 2 H, J = 4 Hz); IR (KBr) ν_{max} 3460, 3134, 1813, 1737, 1540, 1474, 1397, 1220, 1156, 1071, 937, 880, 734, 643 cm^{-1}; EIMS, m/e (relative intensity) 260 ($M^+ - CO_2$, 94), 144 (29), 116 (base), 89 (45), 58 (13); CIMS (2-methylpropane), m/e 261 ($M^+ + H - CO_2$, base).

Anal. Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.95; N, 9.21. Found: C, 70.81; H, 3.65; N, 9.07.

General Procedure for the Preparation of Indole *N*-Carbonyl Compounds with in Situ Generation of Indole-1-carboxylic Acid Anhydride: Preparation of 4g. EDCI·HCl (142 mg, 0.74 mmol) was added to a 25 °C solution of **1** (200 mg, 1.24 mmol) in dry CH_2Cl_2 (5 mL), and the reaction mixture was allowed to stir at 25 °C for 15 min. Allylamine (46 μL, 0.62 mmol) was added, and the resulting mixture was stirred at 25 °C for 15 min. The reaction mixture was poured onto water and extracted with ether (2 × 25 mL). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography (SiO_2, 2 cm × 7 cm, 10% ether–hexane eluant) afforded **4g** (108 mg, 124 mg theoretical, 87%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1 H, J = 8 Hz), 7.60 (d, 1 H, J = 8 Hz), 7.45 (d, 1 H, J = 3 Hz), 7.25 (m, 2 H), 6.61 (d, 1 H, J = 3 Hz), 5.95 (dddt, 1 H, J = 17, 11, 6, 1 Hz), 5.63 (br s, 1 H), 5.30 (d, 1 H, J = 17 Hz), 5.23 (d, 1 H, J = 11 Hz), 4.10 (dt, 2 H, J = 6, 1 Hz); IR (film) ν_{max} 3346, 3142, 3115, 3052, 2925, 1674, 1534, 1474, 1327, 1294, 1153, 1094, 990, 803, 719 cm^{-1}; EIMS, m/e (relative intensity) 200 (M^+, 25), 117 (base), 109 (17), 95 (5), 89 (20), 63 (11); CIMS (2-methylpropane), m/e 201 ($M^+ + H$, base); HRMS, m/e 200.0947 ($C_{12}H_{12}N_2O$ requires 200.0950).

General Procedure for the Preparation of Indole *N*-Carbonyl Compounds Using Indole-1-carboxylic Acid Anhydride (2): Preparation of 4e. A solution containing the sodium salt of phenol [generated in THF (1 mL) at 25 °C from phenol (0.72 mmol, 68 mg) and NaH (0.72 mmol, 29 mg of 60% mineral oil dispersion)] was added to a 25 °C solution of indole-1-carboxylic acid anhydride (**2**, 0.86 mmol, 261 mg) in THF (2 mL), and the resulting mixture was allowed to stir for 15 min. The reaction mixture was poured onto water and extracted with ether (2 × 25 mL). The combined ether extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography (SiO_2, 3 cm × 10 cm, 10% ether–hexane eluant) afforded **4e** (160 mg, 171 mg theoretical, 93%) as a white solid: mp 95–96 °C (hexane, white needles); ^{1}H NMR ($CDCl_3$) δ 8.23 (d, 1 H, J = 8 Hz), 7.75 (d, 1 H, J = 3 Hz), 7.64 (d, 1 H, J = 8 Hz), 7.42 (m, 2 H), 7.32 (m, 5 H), 6.68 (d, 1 H, J = 3 Hz); IR (KBr) ν_{max} 3069, 1753, 1585, 1472, 1328, 1296, 1146, 1008, 995, 881, 771, 610 cm^{-1}; EIMS, m/e (relative intensity) 237 (M^+, base), 193 (5), 144 (57), 116 (73), 89 (28), 77 (16), 63 (8); CIMS (2-methylpropane), m/e 238 ($M^+ + H$, base); HRMS, m/e 237.0788 ($C_{15}H_{11}NO_2$ requires 237.0790).

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Registry No. **1**, 13884-13-4; **2**, 109241-96-5; **3a**, 1003-29-8; **3b**, 1193-62-0; **3c**, 99-76-3; **3d**, 106-44-5; **3e**, 108-95-2; **3f**, 62-53-3; **3g**, 107-11-9; **3h**, 100-51-6; **3i**, 108-98-5; **3j**, 1336-21-6; **3k**, 1202-04-6; **4a**, 109242-01-5; **4b**, 109242-02-6; **4c**, 109242-03-7; **4d**, 109242-04-8; **4e**, 74117-31-0; **4f**, 16036-21-8; **4g**, 109241-97-6; **4h**, 109241-98-7; **4i**, 109241-99-8; **4j**, 13307-58-9; **4k**, 109242-00-4; indole, 120-72-9.

Supplementary Material Available: Experimental details, full spectral characterization, and physical properties of **4a–d,f,h,i–k** (4 pages). Ordering information is given on any current masthead page.