Novel electrophilic ipso acylation – detosylation reaction of pyrroles[1]

Erin T. Pelkey and Gordon W. Gribble

Abstract: A pyrrole and two pyrroloindoles that are substituted with a *p*-toluenesulfonyl group undergo an ipso acylation – detosylation reaction with acid chlorides and aluminum chloride to afford the corresponding acyl-substituted pyrroles and pyrroloindoles.

Key words: pyrrole, pyrroloindole, ipso acylation, detosylation, Friedel–Crafts reaction.

Résumé : Sous l'action de chlorures d'acides et de chlorure d'aluminium, un pyrrole et deux pyrroindoles substitués par un groupe *p*-toluènesulfonyle subissent des réactions d'acétylation-détosylation ipso qui conduisent à la formation des pyrroles et pyrroindoles correspondants substitués par un groupe acyle.

Mots clés : pyrrole, pyrroindole, acétylation ipso, détosylation, réaction de Friedel–Crafts.

[Traduit par la Rédaction]

Introduction

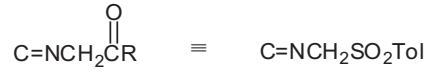
Whereas electrophilic ipso substitution (1) of aromatic and heteroaromatic compounds, including organosilanes (2), organostannanes (3), and several other substrates (4), is well-documented, there appear to be no examples of organosulfones undergoing electrophilic ipso substitution. For example, treatment of 3-phenyl-4-(*p*-toluenesulfonyl)furan with acetyl chloride and $AlCl_3$ gives only the expected electrophilic product, 2-acetyl-3-phenyl-4-(*p*-toluenesulfonyl)furan (5). On the other hand, free radical ipso stannylation – detosylation reactions of 1-(phenylsulfonyl)-2-(*p*-toluenesulfonyl) indole and related heterocycles have been described (6).

Results and discussion

In connection with our interest in the closely related Barton–Zard (7), van Leusen (8), and Montforts (9) syntheses of pyrroles (10), we had occasion to examine the Friedel–Crafts acylation of 4-ethyl-2-(*p*-toluenesulfonyl)pyrrole (**4**). This compound was readily prepared by treating either 2-nitrobutyl acetate (**1**) (11) or 2-nitro-1-butene (**2**) (12) with TosMIC (**3**) (13) and DBU in the presence of isopropanol Scheme 1). Treatment of **4** with acetyl chloride in the presence of aluminum chloride affords 2-acetyl-4-ethylpyrrole (**5**) and not the expected 2-acetyl-3-ethyl-5-(*p*-toluenesulfonyl)pyrrole (**6**). The characteristic odor of *p*-toluenesulfonyl chloride (**7**) in the reaction mixture was indicative of this novel transformation. To confirm the regiochemistry of **5**, we synthesized 2-acetyl-3-ethylpyrrole (**8**) by hydrolysis (K_2CO_3, MeOH, reflux, 78%) of the known 2-acetyl-3-ethyl-1-(phenylsulfonyl)pyrrole (14). Direct comparison of these two pyrroles reveals that the product of the acetylation of **4** was clearly **5** and not **8**. We view this ipso acylation – detosylation reaction as involving ipso electrophilic attack at C-5 in **4** followed by chloride attack on the sulfonyl group to give *p*-toluenesulfonyl chloride and pyrrole **5**.

This ipso acylation – detosylation was extended to the synthesis of acylated pyrroloindoles (Scheme 2). Thus, treatment of pyrrolo[2,3-*b*]indole **10** and pyrrolo[3,4-*b*]indole **13** with acetyl chloride and valeryl chloride in the presence of aluminum chloride affords the acylated analogues **11** and **14**, respectively. Pyrroloindoles **10** and **13** were synthesized with TosMIC from indoles **9** and **12**, respectively, according to our earlier method (10).

In summary, we have discovered a novel electrophilic ipso acylation – detosylation reaction of α-tosylpyrroles. In the context of van Leusen and Barton–Zard pyrrole syntheses, the reagent TosMIC (**3**) can be viewed as a synthetic equivalent for α-isocyanoketones (**15**). Compounds related to **15** have previously been generated from α-metalated oxazoles (15), but they have not been employed in these pyrrole ring syntheses.



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Dedicated to Dr. Alfred Bader, organic chemistry pioneer and art connoisseur extraordinaire. Thank you for giving us decades of wonderful service and for rejuvenating our appreciation of art.

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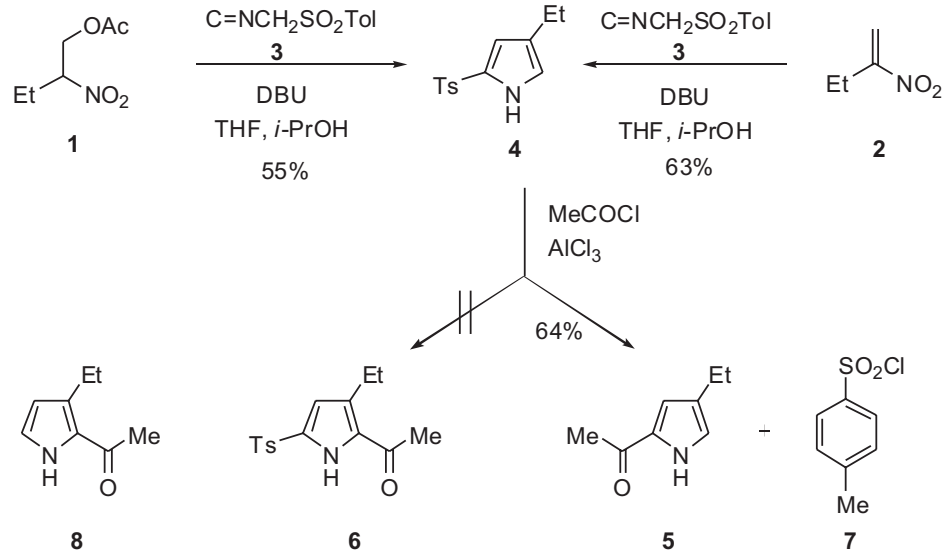
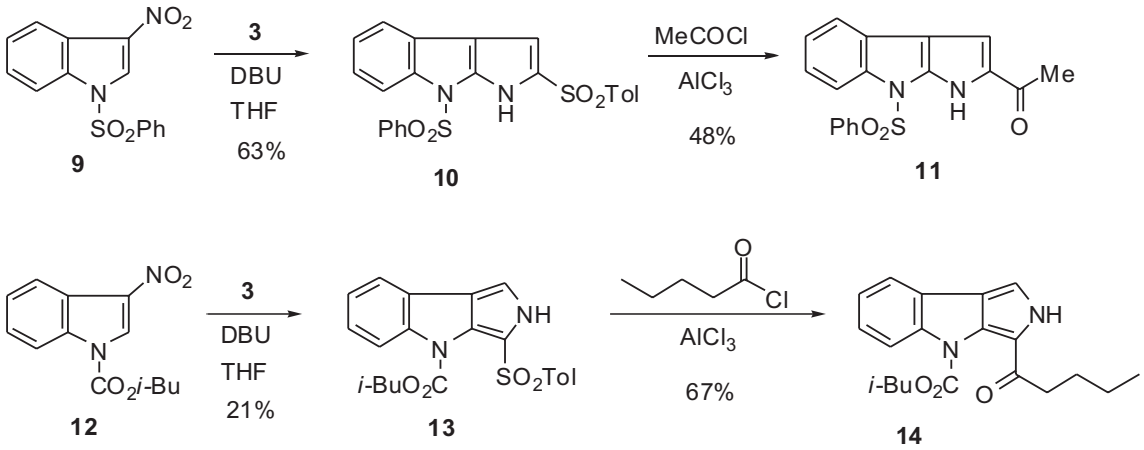
Scheme 1.



Scheme 2.



Experimental

Melting points were determined using open capillary tubes and are uncorrected. Thin-layer chromatography (TLC) was performed on regular TLC plates. Visualization of developed plates was achieved with a 254 nm UV lamp and (or) with iodine. Flash chromatography utilized 230–400 mesh silica gel 60. ^{1}H NMR and ^{13}C NMR were run at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm using the solvent residual proton or carbon signal ($CDCl_3$: H, 7.27, C, 77.23) as an internal reference. The apparent multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), broad (br)), number of protons, and coupling constants (in Hz) are reported in that order in parenthesis after the chemical shift. Infrared spectra (IR) are reported in reciprocal centimeters and were obtained using neat compounds (neat), solid KBr pellets (KBr), polyethylene IR cards (PE), or polytetrafluoroethylene IR cards (PTFE). High-resolution mass spectrometry (HRMS) was performed at the University of Illinois (Urbana-Champaign, Illinois) mass spectrometry laboratory or by the SOCAL Mass Spectrometry Facility at the University of California (Riverside, California). Elemental analyses were performed by Atlantic Microlabs, Inc. (Norcross, Georgia). Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium-benzophenone ketyl. Diisopropylamine, dichloromethane, xylenes, and triethylamine were distilled from calcium hydride. Acetyl chloride, hexanoyl chloride, trimethylsilyl chloride, and valeryl chloride were distilled from 0.1% quinoline. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. All reactions were performed under a positive nitrogen atmosphere with magnetic stirring unless otherwise noted. All glassware was oven-dried at >130 °C and allowed to cool in a desiccator (Drierite®) before assembly under positive nitrogen.

2-Nitro-1-butanol

A modification of a literature procedure was utilized (11). To a 0 °C stirred solution of sodium hydroxide (4.20 g, 105 mmol) dissolved in distilled water (40 mL) was added 1-nitropropane (8.91 g, 100 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature (rt) for 1 h. Upon recooling to 0 °C, the reaction mixture was treated with an aqueous solution of formalin

(37%, 8.52 g, 105 mmol) dropwise via addition funnel over 10 min and then the reaction mixture was stirred at rt for 7 h. Upon recooling to 0 °C, the reaction mixture was treated with acetic acid (6.60 g, 110 mmol) dropwise and stirred for 3 h. The aqueous solution was extracted with ether (5 × 50 mL) and the combined organic extracts were washed with brine (200 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil (20 g) that was purified by vacuum distillation through a Vigreux column. The desired product was obtained as a colorless oil. Yield: 6.57 g, 55.1 mmol, 55%; bp 124 to 125 °C at 10 Torr (1 Torr = 133.322 4 Pa) (lit. value (11) bp 90–92 °C at 3 Torr). ^{1}H NMR ($CDCl_3$) δ: 4.51–4.59 (m, 1H) 3.89–4.10 (m, 2H), 1.81–2.06 (m, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 90.8, 63.1, 23.5, 10.4.

2-Nitrobutyl acetate (1)

A modification of the literature procedure for synthesizing β-nitroacetates was utilized (16). To a 0 °C stirred solution of 2-nitro-1-butanol (5.59 g, 47.0 mmol) dissolved in CH_2Cl_2 (50 mL) was added acetic anhydride (5.72 g, 56.0 mmol) followed by *p*-toluenesulfonic acid monohydrate (380 mg, 2.0 mmol). The reaction mixture was stirred at 0 °C and then at rt for 8 h. Removal of the solvent in vacuo gave a residue (10 g) that was purified by vacuum distillation through a Vigreux column. The desired product **1** was obtained as a light yellow oil. Yield: 6.57 g, 40.1 mmol, 86%; bp 88 to 89 °C at 4 Torr (lit. value (11) bp 70–72 °C at 2 Torr). ^{1}H NMR ($CDCl_3$) δ: 4.62–4.69 (m, 1H), 4.41–4.43 (m, 2H), 2.07 (s, 3H), 1.80–2.06 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 170.5, 87.8, 63.8, 23.9, 20.8, 10.2.

2-Nitro-1-butene (2) (Caution: Lachrymator and foul smelling)

A modification of the literature procedure for the synthesis of 2-nitropropene was utilized (17). A round-bottomed flask (100 mL) fitted with a Vigreux column and short-path distillation apparatus was charged with 2-nitro-1-butanol (11.9 g, 0.100 mol) and phthalic anhydride (29.6 g, 0.200 mol) and was partially evacuated (under water aspirator pressure). The reaction mixture was heated in an oil bath to 150 °C for 30 min and then to 200 °C. The desired product **2** distilled over with water into an ice-cooled receiving flask. The aqueous layer was separated and the organic layer was dried over sodium sulfate. The desired product **2** was obtained as a blue-green oil. Yield: 4.48 g, 0.0443 mol, 44%; bp 76–84 °C at 40 Torr (lit. value (12) bp 108 °C at 61 Torr). IR (neat, cm^{-1}) υ_{max}: 3132, 2980, 2942, 2882, 1524, 1465, 1436, 1347, 1258. ^{1}H NMR ($CDCl_3$) δ: 6.44 (s, 1H), 5.55 (s, 1H), 2.64 (q, J = 7.2 Hz, 2H,), 1.18 (t, J = 7.2 Hz, 3H,). ^{13}C NMR ($CDCl_3$) δ: 159.8, 116.3, 23.6, 11.8.

4-Ethyl-2-(*p*-toluenesulfonyl)pyrrole (4)

To a rt stirred solution of 2-nitro-1-butene (**2**) (202 mg, 2.00 mmol) and tosylmethyl isocyanide (**3**) (586 mg, 3.00 mmol) dissolved in THF (3 mL) and 2-propanol (3 mL) was added a solution of DBU (457 mg, 3.00 mmol) dissolved in THF (3 mL) and 2-propanol (3 mL). The reaction mixture was stirred at rt for 20 h. Removal of the solvent in vacuo gave a brown oil (1.8 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 1:1; CH_2Cl_2–hexanes, 3:1). After eluting a brightly colored yellow impurity (R_f 0.38; CH_2Cl_2–hexanes, 3:1), the desired product **4** was obtained as a yellow amorphous solid. Yield: 372 mg, 80% pure by ^{1}H NMR, 1.25 mmol, 63% yield based on NMR integration. Recrystallization (CH_2Cl_2–hexanes, 1:4) gave **4** as off-white needles; mp 94 to 95 °C. R_f 0.15 (CH_2Cl_2–hexanes, 3:1). IR (PTFE, cm^{-1}) υ_{max}: 3306 (NH), 2964, 2924, 2872, 1595, 1494, 1440, 1379, 1301, 1202, 1146. ^{1}H NMR ($CDCl_3$) δ: 8.90 (br s, 1H), 7.80–7.83 (m, 2H), 7.26 (m, 2H), 6.70–6.75 (m, 2 H), 2.45 (q, 2H, J = 7.5 Hz), 2.39 (s, 3H), 1.15 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 143.9, 139.9, 130.0, 129.0, 127.7, 127.0, 121.1, 114.8, 21.7, 20.0, 15.0. MS *m*/*z* (%): 250 (M^+ + 1), 249 (M^+), 234 (100%), 184, 170, 142, 127, 110, 91, 78, 65. Anal. calcd. for $C_{13}H_{15}NO_2S$: C 62.63, H 6.06, N 5.62, S 12.83; found: C 62.57, H 6.05, N 5.56, S 12.95.

2-Acetyl-4-ethylpyrrole (5)

To a 0 °C stirred suspension of aluminum chloride (333 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) was added freshly distilled (from quinoline) acetyl chloride (79 mg, 1.00 mmol) and the mixture was stirred for 15 min and then treated with a solution of 4-ethyl-2-(*p*-toluenesulfonyl)pyrrole (**4**) (125 mg, 0.500 mmol) dissolved in CH_2Cl_2 (5 mL) dropwise. The reaction mixture was stirred at 0 °C for 1 h and then was poured onto ice (20 g). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (60 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave an orange oil (0.3 g) that was purified by flash chromatography (hexanes; CH_2Cl_2). The title compound **5** was obtained as a yellow oil. Yield: 44 mg, 0.32 mmol, 64%. R_f 0.16 (CH_2Cl_2–EtOAc, 10:1). UV (EtOH) λ_{max} (nm): 208, 250, 302. IR (PTFE, cm^{-1}) υ_{max}: 3257 (NH), 2960, 2920, 2851, 1633 (C=O), 1568, 1479, 1432, 1397, 1322. ^{1}H NMR ($CDCl_3$) δ: 9.82 (br s, 1H), 6.77–6.87 (m, 2H), 2.52 (q, 2H, J = 7.5 Hz), 2.42 (s, 3H), 1.17–1.26 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 188.1, 132.0, 128.6, 122.8, 116.5, 25.5, 20.0, 15.4. MS *m*/*z* (%): 138 (M^+ + 1), 137 (M^+), 122 (100%), 104, 94, 77, 67. HRMS *m*/*z* calcd. for $C_8H_{11}NO$: 137.0841 (M^+); found: 137.0841.

2-Acetyl-3-ethylpyrrole (8)

To a rt stirred solution of 3-ethyl-2-acetyl-1-(phenylsulfonyl)pyrrole (14) (83 mg, 0.30 mmol) dissolved in methanol (5 mL) was added potassium carbonate (170 mg, 1.2 mmol) and the reaction mixture was heated to reflux for 7 h and then allowed to cool to rt. Removal of the solvent in vacuo gave an orange oil (0.5 g) that was partitioned between distilled water (20 mL) and ether (20 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine (60 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil (40 mg) that was purified by flash chromatography (hexanes; CH_2Cl_2). The desired product **8** was obtained as a light yellow amorphous solid. Yield: 32 mg, 0.23 mmol, 78%; mp 64 to 65 °C. R_f 0.18 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 206, 292. IR (PTFE, cm^{-1}) υ_{max}: 3271 (NH), 2967, 1622 (C=O), 1532, 1478, 1407, 1325, 1201, 1136. ^{1}H NMR ($CDCl_3$) δ:

9.43 (br s, 1H), 6.92–6.94 (m, 1H), 6.17–6.19 (m, 1H), 2.82 (q, 2H, J = 7.5 Hz), 2.47 (s, 3H), 1.30 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 187.9, 134.2, 123.3, 111.5, 111.4, 28.0, 21.3, 15.1. MS m/z (%): 138 (M^+ + 1), 137 (M^+), 122 (100%), 94, 80, 67. HRMS m/z calcd. for $C_8H_{11}NO$: 137.0841 (M^+); found: 137.0842.

1,8-Dihydro-4-(phenylsulfonyl)-2-(*p*-toluenesulfonyl)pyrrolo[2,3-*b*]indole (10)

To a stirred solution of 3-nitro-1-(phenylsulfonyl)indole (**9**) (18) (151 mg, 0.500 mmol) dissolved in THF (10 mL) was added a solution of tosylmethyl isocyanide (**3**) (117 mg, 0.600 mmol) dissolved in THF (5 mL) followed by neat DBU (183 mg, 1.20 mmol). The clear yellow reaction mixture was stirred at rt for 22 h. Removal of solvent in vacuo gave a crude orange oil (500 mg) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 3:1; CH_2Cl_2). The desired product **10** was obtained as a white amorphous solid (150 mg). Trituration (hexanes, 2 × 5 mL) gave **10** as a gray flaky solid. Yield: 142 mg, 0.315 mmol, 63%; mp 212–214 °C (dec). Two recrystallizations (CH_2Cl_2–cyclohexane, 2:1) gave **10** as white crystals; mp 236–238 °C. R_f 0.50 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 210, 274 (sh), 300, 346 (sh). IR (KBr, cm^{-1}) υ_{max}: 3256 (NH), 2928, 1540, 1528, 1447, 1419, 1374, 1318, 1181. ^{1}H NMR ($CDCl_3$) δ: 9.78 (bs, 1H), 7.88–7.92 (m, 3H), 7.74–7.76 (m, 2H), 7.48–7.54 (m, 2H), 7.22–7.37 (m, 6H), 7.11 (d, 1H, J = 1.8 Hz), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 144.3, 139.6, 138.5, 137.6, 136.4, 134.8, 130.2, 129.6, 128.8, 127.2, 126.9, 125.0, 124.6, 124.3, 120.1, 114.8, 113.4, 107.6, 21.8. MS m/z (%): 473.1 $(M + Na)^+$. Anal. calcd. for $C_{23}H_{18}N_2O_4S_2$: C 61.32, H 4.03, N 6.22, S 14.23; found: C 61.35, H 4.04, N 6.23, S 14.36.

2-Acetyl-1,8-dihydro-8-(phenylsulfonyl)pyrrolo[2,3-*b*]indole (11)

To a 0 °C stirred suspension of aluminum chloride in CH_2Cl_2 (5 mL) was added acetyl chloride (79 mg, 1.0 mmol) and the mixture was stirred for 15 min. The reaction mixture was treated with a solution of 1,8-dihydro-2-(*p*-toluenesulfonyl)-4-(phenylsulfonyl)pyrrolo[2,3-*b*]indole (**10**) (225 mg, 0.500 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0 °C for 2 h and then at rt for 30 min. The reaction was poured onto ice (20 g) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a yellow oil (0.6 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 1:1; CH_2Cl_2–hexanes, 3:1). The desired product **11** was obtained as a white amorphous solid. Yield: 82 mg, 0.24 mmol, 48%; mp 222–225 °C. Recrystallization (CH_2Cl_2–hexanes) gave **11** as light brown crystals; mp 230 to 231 °C. R_f 0.18 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 206, 224, 254 (sh), 332. IR (PTFE, cm^{-1}) υ_{max}: 3304 (NH), 2917, 2851, 1633, 1555, 1488, 1440, 1380, 1285, 1201, 1171. ^{1}H NMR ($CDCl_3$) δ: 9.87 (br s, 1H), 7.93–7.96 (m, 1H), 7.81–7.85 (m, 2H), 7.27–7.59 (m, 6H), 7.11 (d, 1H, J = 1.5 Hz), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 187.9, 139.1, 139.0, 136.9, 134.7, 132.9, 129.6, 127.0, 124.9, 124.7, 124.4, 120.0, 114.9, 113.5, 108.2, 25.3. MS m/z (%): 338 (M^+), 197 (100%), 169, 155, 127, 101, 77. Anal. calcd. for $C_{18}H_{14}N_2O_3S$: C 63.89, H 4.17, N 8.28, S 9.47; found: C 64.04, H 4.07, N 8.20, S 9.34.

2-Methyl-1-propyl 2,4-dihydro-3-(*p*-toluenesulfonyl)pyrrolo[3,4-*b*]indole-4-carboxylate (13)

To a rt stirred solution of 2-methyl-1-propyl 3-nitroindole-1-carboxylate (**12**) (18) (1.84 g, 7.00 mmol) and tosylmethyl isocyanide (**3**) (1.56 g, 8.00 mmol) dissolved in THF (50 mL) was added DBU (1.22 g, 8.00 mmol) and the reaction mixture was stirred at rt for 20 h. Removal of the solvent in vacuo gave a brown oil (4 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 3:1; CH_2Cl_2). The desired product **13** was obtained as a brown amorphous solid (615 mg, 1.50 mmol, 21%) that was purified by a second round of column chromatography (hexanes; CH_2Cl_2–hexanes, 1:1). The yellow powder thus obtained was recrystallized (CH_2Cl_2–hexanes) to give **13** as fine yellow needles; mp 177 to 178 °C. R_f 0.23 (CH_2Cl_2). UV (EtOH) λ_{max} (nm): 206, 222 (sh), 254 (sh), 278, 315 (sh), 324. IR (PTFE, cm^{-1}) υ_{max}: 3283 (NH), 2958, 1731 (C=O), 1595, 1515, 1448, 1417, 1379, 1317, 1199, 1139. ^{1}H NMR ($CDCl_3$) δ: 9.60 (br s, 1H), 8.32 (br s, 1H), 8.24–8.26 (m, 1H), 7.89 (d, 2H, J = 8.1 Hz), 7.34–7.49 (m, 2H), 7.24 (d, 2H, J = 8.1 Hz), 7.03 (br s, 1H), 4.23 (d, 2H, J = 4.8 Hz), 2.35 (s, 3H), 2.14 (br s, 1H), 1.06 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 151.4, 144.2, 143.2, 139.7, 131.4, 130.1, 127.4, 126.6, 123.8, 122.8, 121.5, 120.0, 116.1, 115.5, 107.2, 73.1, 28.1, 21.7, 19.3. HRMS m/z calcd. for $C_{22}H_{22}N_2O_4S$: 410.1300 (M^+); found: 410.1294. Anal. calcd. for $C_{22}H_{22}N_2O_4S$: C 64.37, H 5.40, N 6.82, S 7.81; found: C 64.46, H 5.51, N 6.85, S 7.76.

2-Methyl-1-propyl 2,4-dihydro-3-valerylpyrrolo[3,4-*b*]-indole-4-carboxylate (14)

To a 0 °C stirred suspension of aluminum chloride (200 mg, 1.50 mmol) in CH_2Cl_2 (5 mL) was added freshly distilled (from 0.1% quinoline) valeryl chloride (72 mg, 0.60 mmol) and this was stirred for 15 min. The reaction mixture was treated with a solution of 2-methyl-1-propyl 2,4-dihydro-3-(*p*-toluenesulfonyl)pyrrolo[3,4-*b*]indole-1-carboxylate (**13**) (123 mg, 0.300 mmol) dissolved in CH_2Cl_2 (10 mL) dropwise. The reaction mixture was stirred at 0 °C for 15 min and then was poured onto ice (20 g). The aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a tan amorphous solid (0.2 g) that was purified by flash chromatography (hexanes; CH_2Cl_2–hexanes, 1:1; CH_2Cl_2–hexanes, 3:1). The desired product **14** was obtained as an off-white amorphous solid (68 mg, 0.20 mmol, 67%, mp 166–168 °C). Recrystallization (EtOAc–hexanes) gave **14** as white needles; mp 173 to 174 °C. R_f 0.48 (H_2Cl_2–MeOH, 98:2). UV (EtOH) λ_{max} (nm): 206, 233 (sh), 246 (sh), 277 (sh), 286, 311 (sh), 344 nm. IR (KBr) υ_{max} (cm^{-1}): 3236 (NH), 2956, 2870, 1728 (C=O), 1627 (C=O), 1506, 1460, 1402, 1390, 1319, 1268, 1219. ^{1}H NMR ($CDCl_3$) δ: 10.04 (br s, 1H), 8.43 (br s, 1H), 8.00–8.02 (m, 1H), 7.43–7.48 (m, 1H), 7.33–7.38 (m, 1H), 7.13 (br s, 1H), 4.27 (d, 2H, J = 6.3 Hz), 3.12 (t, 2H, J = 7.2 Hz), 2.12–2.22 (m, 1H), 1.82–1.92 (m, 2H), 1.48–1.60 (m, 2H), 1.10 (d, 6H, J =

6.9 Hz), 1.02 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 190.1, 151.6, 143.4, 131.8, 126.8, 123.5, 122.6, 122.5, 121.0, 118.5, 116.3, 107.5, 73.2, 40.5, 28.2, 26.7, 22.8, 19.4, 14.3. MS *m/z* (%): 340 (M^+, 100%), 298, 283, 242, 198, 183, 156, 127, 101, 77. Anal. calcd. for $C_{20}H_{24}N_2O_3$: C 70.57, H 7.11, N 8.23; found: C 70.32, H 7.11, N 8.13.

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