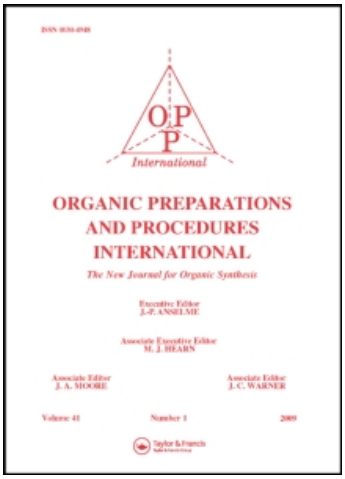

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ALTERNATE SYNTHESES OF PRODAN AND ACRYLODAN

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ALTERNATE SYNTHESES OF PRODAN AND ACRYLODAN

Submitted by Steven S. Silvonek, Carl B. Giller and Christopher J. Abelt*
(09/23/05)

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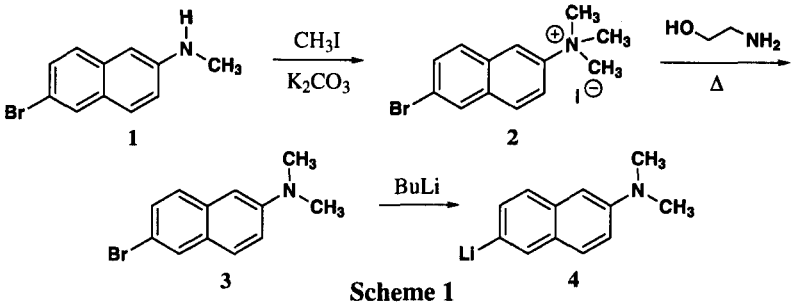
Prodan [6-propionyl-2-(dimethylamino)naphthalene, **6**] was synthesized by Weber and Farris in 1979 as a fluorescent probe of micropolarity.[1] The prodan moiety was attached to thiols and amines in proteins using acrylodan [6-acryloyl-2-(dimethylamino)naphthalene, **12**].[2,3] The covalently bound chromophore is a fluorescent molecular sensor of the labeled sites.[4-6]

We have been interested in preparing derivatives of prodan and acrylodan to understand the nature of the emissive intramolecular charge-transfer state. The literature synthesis of prodan is not convergent.[1] The first step sets the identity of the carbonyl group through a Friedel-Crafts acylation, while aromatic substitution with lithium dimethylamide creates the amine group. Application of this literature method to the preparation of prodan derivatives would require completely separate routes for each one. Acrylodan is prepared from prodan[2] *via* a selenation/oxidation/elimination sequence.[7] Recently in this *Journal*, López and coworkers reported a different method for the synthesis of prodan derivatives where the identity of both the carbonyl and amino groups is established later in the synthetic route.[8] In particular, the carbonyl group is generated by nucleophilic addition of an aryllithium to an aliphatic nitrile. Since organolithiums are strong bases, their addition to aliphatic nitriles is often complicated by the competing α-hydrogen abstraction reaction, which may explain the low yields for the addition step (14-36%) reported by López. This contribution describes an alternate route that avoids these problems and provides a direct preparation of acrylodan.

As with the procedure of López, our alternate preparation began with **4**, the aryllithium derived from **3**, which was prepared by an alkylation/dealkylation route rather than by the acylation/reduction procedure of López. Reaction of the amine **1** with excess MeI afforded the

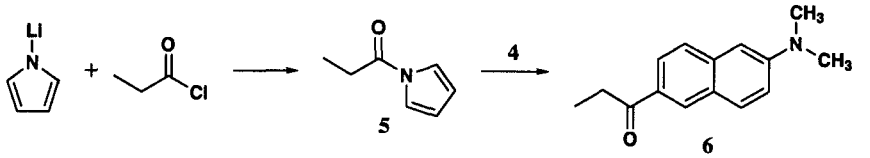
quaternary salt **2**, which was demethylated with ethanolamine to give **3**.[9] The quaternization is a high yield process, and the ammonium salt was conveniently recrystallized from water and the demethylation is also a simple, high yield procedure (*Scheme 1*).



Scheme 1

Our route to prodan derivatives used the acylpyrrole method for preparation of ketones.[10,11] The pyrrole group enhances the electrophilicity of the carbonyl group compared to other tertiary amides. Nucleophilic addition of aryllithiums can occur at –78°C. At this temperature, the carbinol intermediate is stable thereby preventing the diarylation that occurs with esters and other carboxylic acid derivatives. In contrast, nucleophilic addition with nitriles requires prolonged heating, even with a copper catalyst.[12] When one of the ketone groups is aromatic, elimination of the pyrrole group occurs with protonation and warming to room temperature.[10]

The application of this method to the preparation of prodan was straightforward. The requisite *N*-propionylpyrrole (**5**) was prepared by the nucleophilic addition of lithium pyrrolide to propionyl chloride (*Scheme 2*).[13] Nucleophilic addition of aryllithium **4** to **5** at –78°C

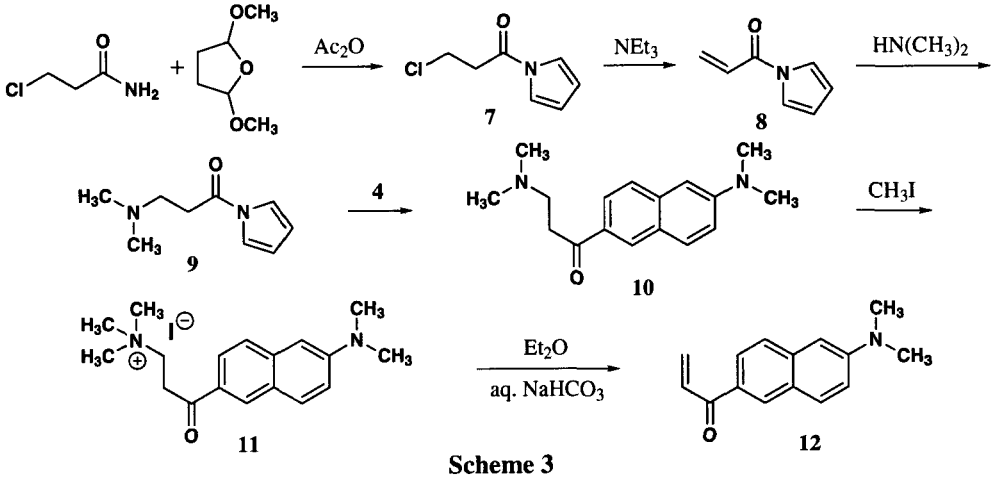


Scheme 2

afforded prodan in (**6**) 47% yield after work-up and recrystallization. The side-product resulting from hydrogen abstraction reaction of **5** by **4** to give 2-(dimethylamino)naphthalene was a minor process, comprising only 15% of the product mixture. Some of the side-product could have arisen from reaction of **4** with proton sources other than **5**.

The preparation of acrylodan using the pyrrole methodology was more complicated (*Scheme 3*). The 3-dimethylamino derivative **9** was determined to be the reactant of choice after a number of other methods proved ineffective. For example, the direct route using *N*-acryloylpyrrole (**8**) gave only polymers, a result which was not surprising since acrylates are well known to polymerize under basic conditions.[14,15] Pyrrole **9** was prepared in three steps from 3-chloropropionamide as shown in *Scheme 3*. The reaction of **9** with the aryllithium **4** proceeded

by the desired nucleophilic substitution to afford **10**, a Mannich base. We note that the Mannich route into **10** from **4** would require two steps since the reactant in the Mannich reaction is 6-acetyl-2-(dimethylamino)naphthalene. Quaternization of **10** with methyl iodide gave **11**; organic by-products, including pyrrole and 2-(dimethylamino)naphthalene, were conveniently removed by washing the salt **11** with ether. The aromatic dimethylamino group is much less nucleophilic and does not complicate the reaction. Stirring the ammonium salt **11** in a two-phase system of aqueous bicarbonate and ether at room temperature generated the enone.[16] Thus, the conversion of **10** to **12** was essentially a work-up procedure in the preparation of **10**.



Scheme 3

The acylpyrrole substitution method was used to prepare prodan and acrylodan from a common precursor **3**. These convergent routes are amenable for the preparation of prodan derivatives. We plan to exploit these routes for the synthesis of prodan molecular sensors.

EXPERIMENTAL SECTION

Mps were determined on a Mel-Temp capillary melting point apparatus and are uncorrected.[1]H NMR spectra were obtained on a Varian Mercury VX-400 spectrometer. Combustion analyses were performed by Desert Analytics. THF was distilled from sodium metal.

6-Bromo-2-(dimethylamino)naphthalene (3).- Bromonaphthylamine **1** (14.0 g, 59 mmol) was dissolved in DMF (75 mL). To this solution was added K_2CO_3 (16.6 g, 120 mmol) followed by methyl iodide (17.04 g, 120 mmol). The reaction flask was loosely stoppered and the mixture was stirred at room temperature overnight. The next day the preciptated solid was collected. The solid obtained was washed first with acetone, then water. The powdered solid was recystallized from water (500 mL) to afford (6-bromonaphthalen-2-yl)trimethylammonium iodide (**2**) as white plates (18.56 g, 80%). The ammonium salt **2** (8.75 g, 22.3 mmol) was combined with ethanolamine (20 mL) and heated to 150°C under nitrogen for 1 hour. The mixture was cooled to ~80°C, then poured slowly into ice water (500 mL) with stirring. After 10 min, the product was

collected and purified by sublimation under vacuum (0.1 Torr) to give 4.60 g (82%) of white solid, mp 130-131°C, *lit.*[8] 129-130°C.

***N*-Propionylpyrrole (5)**[13].- A solution of pyrrole (6.14 g, 91.5 mmol) in dry THF (125 mL) under Ar was cooled in an ice-bath. A solution of *n*-BuLi (60 mL, 1.6 M in hexanes) was added dropwise at a rate so that the temperature did not rise above 5°C. The solution was stirred for 15 min. Propionyl chloride (8.49 g, 92.5 mmol) was added in portions keeping the temperature below 15°C. The reaction was stirred at room temperature for 2 hrs, then poured into water (500 mL). The mixture was extracted with EtOAc (200 mL). The organic layer was washed twice with aq. HCl (200 mL, 4%) and once with water (200 mL). The layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was distilled under vacuum to yield 5.86 g (52%) of *N*-propionylpyrrole (**5**) as a clear, colorless liquid, bp 37°C (0.1 Torr), *lit.*[13] 78°C (12 Torr); ^{1}H NMR ($CDCl_3$): δ 7.32 (br. s, 2H), 6.29 (t, J = 2.2 Hz, 2H), 2.86 (q, J = 7.3 Hz, 2H), 1.29 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.4, 119.1, 113.1, 28.1, 8.8.

***N*-(3-Chloropropionyl)pyrrole (7)**.- 2,5-Dimethoxytetrahydrofuran (50 mL) was cooled in an ice-bath under N_2. Acetic anhydride (8.89 g, 87.1 mmol) was added, and the solution is stirred at 0°C for 10 min. 3-Chloropropionamide (9.08 g, 84.4 mmol) was then added in one portion and the reaction mixture was heated at 60°C for 2 days. The reaction mixture was allowed to cool and added to an aqueous solution (500 mL) of NaCl (100 g) and Na_2CO_3 (2 g). The solution was stirred rapidly for 15 min then was allowed to settle. The aqueous layer was filtered by gravity. The oily residue caught in the filter paper and that remaining on the beaker were dissolved in 1:1 ethyl acetate/hexanes (100 mL) and washed with brine (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was distilled under vacuum (0.1 Torr) to afford 8.52 g (57%) of *N*-(3-chloropropionyl)pyrrole (**7**), bp 82°C, containing 10% dimethoxytetrahydrofuran. ^{1}H NMR ($CDCl_3$): δ 7.31 (br. s, 2H), 6.32 (t, J = 2.3 Hz, 2H), 3.92 (t, J = 6.7 Hz, 2H), 3.31 (t, J = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 167.4, 119.1, 113.8, 38.3, 37.7. This material was used without further purification. An analytical sample of **7** was prepared by treatment of **8** with two equivalents of trimethylsilyl chloride and one equivalent of H_2O in ether overnight. Aqueous workup and vacuum distillation gave **7** as a waxy white solid, mp 40-41°C, containing trace amounts of water.

Anal. Calcd for $C_7H_8ClNO \cdot 0.09\ H_2O$: C, 52.81; H, 5.18, N, 8.80

Found: C, 52.55; H, 4.99; N, 8.75

***N*-Acryloylpyrrole (8)**[10].- To a solution of *N*-(3-chloropropionyl)pyrrole (**7**, 8.42 g, 90%, 48.9 mmol) in ether (70 mL) was added triethylamine (8.36 g, 82.6 mmol), and the reaction mixture was stirred overnight. The next day, the precipitated triethylamine hydrochloride was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was distilled under vacuum (0.1 Torr) to give **8** as a colorless liquid, bp. 56°C, containing 8% dimethoxytetrahydrofuran (5.30 g, 82%). This material was used without further purification.

***N*-[3-(Dimethylamino)propionyl]pyrrole (9)**.- *N*-Acryloylpyrrole **8** (2.99 g, 24.7 mmol),

dimethylamine solution (12.3 mL, 24.6 mmol, 2M in THF), and 2,6-di-*tert*-butylphenol (50 mg) were combined in a sealed tube under a blanket of argon and heated to 65°C for 1.5 hr. The reaction mixture was allowed to cool to r.t., then concentrated *in vacuo*. The residue was distilled under vacuum (0.1 Torr) to yield 3.86 g. (89%) of **9**, as a colorless liquid containing 5% *N*-acryloylpyrrole. ^{1}H NMR ($CDCl_3$): δ 7.33 (br. s, 2H), 6.30 (br. s, 2H), 3.00 (t, J = 7.2 Hz, 2H), 2.79 (t, J = 7.2 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 169.5, 119.2, 113.4, 54.6, 45.7, 33.4.

This compound was purified by conversion to its HCl salt. Compound **9** (3.74 g, 22.5 mmol) was dissolved in MeOH (20 mL), and the resulting solution was cooled in an ice bath. Conc. aq. HCl (2.0 mL) was added dropwise. After the solid that precipitated had been dissolved by addition of MeOH (40 mL), ether (260 mL) was added dropwise with rapid stirring. The white solid that formed was collected and washed with cold ether. The solid was dried *in vacuo* giving 4.17 g (91%) of the HCl salt as a white solid.

Anal. Calcd. for $C_9H_{15}ClN_2O$: C, 53.33; H, 7.46, N, 13.82. Found: C, 53.53; H, 7.30; N, 13.82.

The free base was generated as a colorless liquid, bp. 95°C (0.1 Torr) from this salt and contains trace amounts of water.

Anal. Calcd. for $C_9H_{14}N_2O$•0.08 H_2O: C, 64.47; H, 8.51, N, 16.71

Found: C, 64.22; H, 8.21; N, 16.46

Prodan (6).- Bromonaphthalene **3** (1.35 g, 5.4 mmol, sublimed just before use) was dissolved in dry THF (40 mL), and the mixture was cooled to –78°C under Ar. *n*-BuLi (3.6 mL, 1.6 M in hexanes, 5.8 mmol) was added dropwise slowly, and the reaction mixture was stirred for 30 min. A solution of **5** (700 mg, 5.68 mmol) in THF (5 mL) was slowly added dropwise. The reaction mixture was stirred and allowed to warm to –45°C over 1.5 hr and then quenched by pouring into water. The aqueous mixture was stirred overnight and the following day, the solid was collected. The solid was sublimed under vacuum giving 790 mg of a mixture of prodan (**6**) and 2-(dimethylamino)naphthalene (85:15). This mixture was recrystallized from ethanol/water to yield prodan as a bright yellow solid (580 mg, 47%, three crops), mp 142-143°C, *lit.*[1] 139-140°C.

Acrylodan (12).- Bromonaphthalene **3** (1.06 g, 4.24 mmol) was dissolved in dry THF (60 mL), and the mixture was cooled to –78°C under argon. *n*-Butyllithium (2.9 mL, 1.6 M in hexanes, 4.6 mmol) was added dropwise slowly. The reaction mixture was stirred for 40 min. A solution of **9** in THF (3 mL) was slowly added dropwise, and the mixture was stirred for 2 hrs and allowed to warm up to –45°C. The mixture was quenched with 50% aq. HOAc (0.5 mL) and allowed to warm to room temperature over several hrs. It was poured into water (200 mL) and extracted with 1:1 ethyl acetate/hexanes (2 x 100 mL). The combined organic extracts were washed with water (2 x 100 mL), dried over $CaCl_2$, and concentrated *in vacuo*. The residue was diluted with ether (30 mL), treated with MeI (690 mg, 4.86 mmol), and the mixture was stirred overnight. The quaternary ammonium salt (**11**) was collected and washed with several portions of ether. It was suspended in water (200 mL) and ether (200 mL). Sodium bicarbonate (7 g, 83 mmol) was added and the mixture was stirred at room temperature for 2 hrs after which all of the solid

dissolved. The layers were separated, and the aqueous layer was extracted with ether (2 x 50 mL). The ethereal layers were combined, dried over $CaCl_2$, and concentrated *in vacuo* to afford acrylodan (**12**) (390 mg, 40% from **3**) as an orangish yellow solid, mp 129-130°C. It was recrystallized from EtOH (20 mL) and water (10 mL) giving 300 mg (two crops), mp 130-131°C, *lit.*[2] 127-128°C.

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