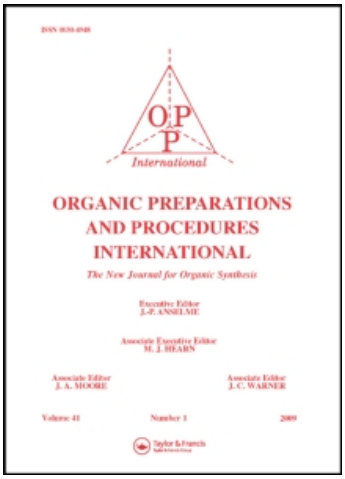

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SYNTHESIS OF 1,9-DIAMIDINIUMACRIDINE AS A POTENTIAL RECEPTOR FOR PHOSPHATE ESTER RECOGNITION

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SYNTHESIS OF 1,9-DIAMIDINIUMACRIDINE AS A POTENTIAL RECEPTOR FOR PHOSPHATE ESTER RECOGNITION

Submitted by (08/11/00)

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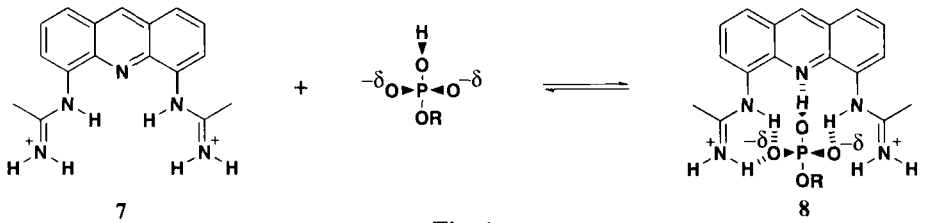
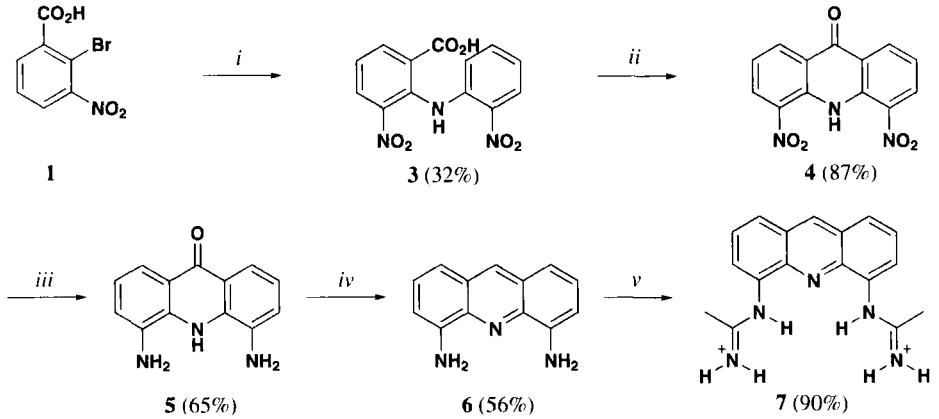
One of the most intriguing topics in biochemistry is the regulation of enzyme structure and function by phosphorylation of serine, threonine, and tyrosine residues.[1] Phosphorylation is the most abundant post-translational modification of proteins and results in covalent but easily reversible regulation. It has been demonstrated that phosphatases play key roles in tumor suppression, the control of normal and neoplastic cell growth, and cell proliferation.[2,3] At the present time there are relatively few examples of synthetic phosphate ester binding receptors.[4] In a continuing effort to design receptors for phosphate recognition,[5-8] 1,9-diamidiniumacridine (**7**) was synthesized in order to test its ability to bind to phosphate mono-esters (**8**) (Fig. 1).



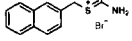
7 8

Fig. 1

The synthesis of compound **7** in five steps (*Scheme 1*) utilized the preparation of diaminoacridines described by Klein and Lahey in 1947.[9] The first step of the synthesis utilized the Ulmann condensation between the aryl bromide **1** and *o*-nitroaniline (**2**) to produce the dinitrodiphenylamine carboxylic acid **3** at 190-200° in an oil bath. Control of the temperature was found to be critical. If the temperature was too low, the reaction did not occur while considerable amount of by-products were formed above 200°. In the second step, the intramolecular acid-catalyzed acylation of **3** gave the dinitroacridone **4** (87%). Compound **5** was then obtained (65%) through the stannous chloride reduction of the nitro groups of compound **4**. The fourth step of the synthesis is reduction of the carbonyl functionality in diaminoacridone **5** using a sodium mercury amalgam producing diaminoacridine **6** (56%). In the final step, the diamidiniumacridine **7** was prepared from the diaminoacridine **6** using S-(2-naphthylmethyl)-thioacetamide hydrobromide in ethanol.[10] Compound **7** was isolated as the bis-trifluoroactetate (TFA) (90%) after reverse phase chromatography.



1 → *i* → **3** (32%) → *ii* → **4** (87%) → *iii* → **5** (65%) → *iv* → **6** (56%) → *v* → **7** (90%)

i) 2-Nitroaniline (**2**), Cu°, Na_2CO_3/K_2CO_3, 300°C, 3 hrs. *ii*) H_2SO_4, 100°C, 1.5 hr. *iii*) HCl, $SnCl_2$, Δ, 3 hrs. *iv*) 5% Na/Hg, 80°C, 4 hrs. *v*)  Ethanol, 25°C, 3 hrs.

Scheme 1

The overall yield for the synthesis of 1,9-diamidiniumacridine (**1**) trifluoroactetate was approximately 10%, with the most inefficient step being the Ulmann coupling reaction. The Pd(II)

catalyzed intermolecular amination of aryl bromides used by Emoto *et al.* in their synthesis of phenazines is presently being investigated to replace the Ulmann coupling reaction.[11]

EXPERIMENTAL SECTION

Capillary melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian Unity Plus 300 MHz NMR spectrometer. Proton spectra were obtained at 300 MHz; carbon spectra were determined at 75.46 MHz; both were referenced to tetramethylsilane (δ = 0.00 ppm). 2-Bromo-3-nitrobenzoic acid and *o*-nitroaniline were purchased from the Aldrich Chemical Company.

2,2'-Dinitrodiphenylamine-6-carboxylic Acid (3).- To a 500-mL beaker was added compound **1** (7.08 g, 28.8 mmol), compound **2** (7.16 g, 51.8 mmol), potassium carbonate (2.01 g, 14.5 mmol), sodium carbonate (3.56 g, 33.6 mmol) and copper dust (0.50 g, 7.9 mmol). The mixture was heated in an oil bath at 192° for 3 hrs.. After the mixture had cooled, boiling water was added, and insoluble salts were removed by gravity filtration. Conc. hydrochloric acid was added to the filtrate until no additional solid precipitated. The brown-yellow precipitate was collected by gravity filtration and thoroughly mixed with 100 mL of a saturated sodium bicarbonate solution. The mixture was filtered to remove any insoluble material. Conc. hydrochloric acid was added to the filtrate until no additional solid precipitated. The bright yellow product was collected by suction filtration and dried to give 2.79 g (32%) of compound **3**, mp 244-246°, *lit.*[9] 246°; ^{1}H NMR (DMSO-d_6): δ 6.96 (d, 1H, J = 8.4 Hz, aromatic), 7.42 (t, 1H, J = 8.0 Hz, aromatic), 7.10 (t, 1H, J = 8.0 Hz, aromatic), 7.45 (t, 1H, J = 14.7 Hz, aromatic), 8.14 (d, 1H, J = 8.0 Hz, aromatic), 8.25 (dd, 2H, J = 8.1 Hz, aromatic). ^{13}C NMR (DMSO-d_6): δ 116.70, 121.03, 122.78, 124.69, 125.57, 129.57, 134.52, 135.01, 135.97, 136.74, 138.23, 142.12, 166.74.

1,9-Dinitroacridone (4).- In a 100-mL round-bottomed flask was added compound **3** (4.85 g, 16.0 mmol) and conc. sulfuric acid (21 mL). The reaction mixture was heated on a steam bath for an hour. The reaction mixture was poured over ice to give a green-yellow precipitate. The precipitate was collected by suction filtration and washed with three, 50-mL portions of cold water. The solid was then washed with boiling saturated sodium bicarbonate until the production of carbon dioxide ceased. The solid was then washed with three, 50-mL portions of boiling water and dried under high vacuum to give 3.95 g (87%) of compound **4**, mp 255-256° *lit.*[9] 256-257°; ^{1}H NMR (DMSO-d_6): δ 7.64 (t, 1H, J = 8.0 Hz, aromatic), 8.77 (d, 1H, J = 7.8 Hz, aromatic), 8.89 (d, 1H, J = 8.1 Hz, aromatic). ^{13}C NMR (DMSO-d_6): δ 121.87, 122.52, 132.12, 134.12, 134.47, 134.87, 174.51.

1,9-Diaminoacridone (5).- To a 100-mL round-bottomed flask was added conc. hydrochloric acid (25 mL). The hydrochloric acid was heated to reflux for 5 minutes, and stannous chloride (7.69 g, 34.1 mmol) was added. The solution was refluxed for an additional 5 minutes and then saturated with hydrogen chloride gas. Compound **4** (2.43 g, 8.50 mmol) was added to the refluxing solution over a

period of one hour. After the addition was complete, the mixture was refluxed for an additional 2 hours. The reaction mixture was cooled to 0°. The precipitate which formed was collected by gravity filtration and washed with three portions of 20 mL of cold ether. The solid was dissolved in boiling water. The mixture was placed in an ice bath, and conc. ammonium hydroxide was added until no additional greenish-yellow solid precipitated. The precipitate was collected by suction filtration and was dissolved in boiling ethanol and any insoluble material was removed by gravity filtration. The solvent was removed from the filtrate under reduced pressure to produce 1.26 g (65%) of compound **5** as an orange crystalline solid, mp >320°, *lit.*[9] 340-342°; ^{1}H NMR (D_2O/DCl): δ 6.59 (d, 2H, J = 8.0 Hz, aromatic), 6.69 (t, 2H, J = 7.3 Hz, aromatic), 7.32 (d, 2H, J = 7.2 Hz, aromatic). ^{13}C NMR (DMSO-d_6): δ 113.03, 115.55, 120.60, 120.99, 129.20, 136.86, 176.69.

1,9-Diaminoacridine (6).- To a 100-mL round-bottomed flask was added 50 mL water and compound **5** (1.06 g, 4.69 mmol). The mixture was heated to 80° and 5% sodium amalgam (37 g) was added over a period of two hours. After the addition was complete, the reaction mixture was heated at 80° for an additional two hours. The reddish solid which formed was collected by suction filtration and washed with three 50-mL portions of cold water. The solid was placed in 20 mL of boiling 30% ethanol/water solution, and any insoluble solid was removed by gravity filtration. The filtrate was placed in the refrigerator. After standing for two days, the precipitate which formed was collected by suction filtration to give 0.55 g (56%) of compound **6** as a golden yellow solid, mp 178°, *lit.*[9] 177°; ^{1}H NMR (D_2O/DCl): δ 7.22 (t, 2H, J = 8.0 Hz, aromatic), 7.56 (d, 2H, J = 7.2 Hz, aromatic), 7.62 (d, 2H, J = 9.0 Hz, aromatic), 8.47 (s, 1H, aromatic). ^{13}C NMR (D_2O/DCl): δ 142.99, 144.06, 145.02, 145.66, 147.31, 156.53, 159.29.

1,9-Diamidiniumacridine (7) *bis*-Trifluoroacetate.- To a 25-mL round-bottomed flask was added compound **5** (50 mg, 0.23 mmol) and 10 mL ethanol. The solution was cooled to 0° in an ice bath. S-2-Naphthylmethyl thioacetimide hydrobromide (1.5 g, 5.0 mmol) was added to the cooled solution. The mixture was stirred for 15 minutes at 0° and then allowed to warm to room temperature over 2 hours. The solvent was removed under reduced pressure and water/ether was used to partition the organics. The water was then lyophilized, and the resulting solid was purified by reverse phase chromatography [water(0.05% TFA):acetonitrile, 0-30% acetonitrile over 30 minutes] to afford 0.11 g (90%) of compound **7** as the *bis* TFA salt, mp > 320°; ^{1}H NMR (2 x $^-$TFA, D_2O): δ 2.49 (s, 6H, CH_3), 7.59 (t, 2H, J = 7.2 Hz, aromatic), 7.87 (s, 1H, aromatic), 8.01 (d, 2H, J = 7.2 Hz, aromatic), 8.35 (d, 2H, J = 7.8 Hz, aromatic), 9.09 (s, 1H, aromatic). ^{13}C NMR (2 x $^-$TFA, D_2O): δ 18.57, 114.15, 118.65, 122.67, 125.23, 126.14, 127.83, 129.94, 130.14, 130.85, 139.42, 143.16, 165.39, 165.98, 166.19, 166.86, 167.50;

Anal. Calcd for $C_{21}F_6H_{19}N_5O_4$: C, 48.55; H, 3.66; N, 13.48. Found: C, 48.42; H, 3.70; N, 13.52.

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A SYNTHESIS OF (*E*)-ω-CARBOXY-2-ALKENOIC ESTERS

Submitted by (8/08/00)

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Substrates bearing differentiated functionality hold great value in organic synthesis. In the course of our studies, we needed access to 10-gram quantities of (*E*)-5-(ethoxycarbonyl)-4-pentenoic acid (**4**), (*E*)-6-(ethoxycarbonyl)-5-hexenoic acid (**5**) and (*E*)-7-(ethoxycarbonyl)-6-heptenoic acid (**6**). These compounds are known and have proven useful in a number of synthetic applications.[1-3] For example, **4** and **5** have been explored as annulating agents[1b,1c,2] while **6** has been employed in the synthesis of a leukotriene analogue.[3] In prior reports, these compounds were prepared by multistep