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A PRACTICAL SYNTHESIS OF *N-p*-ANISYL-*N*-METHYL-AMINO-3-(9-ANTHRYL)-PROPANE: AN EXCIPLEX FLUORESCENCE 'THERMOMETER'

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Abstract: A practical synthesis of *N-p*-anisyl-*N*-methyl-amino-3-(9-anthryl)-propane from 9-anthraldehyde is described. All the intermediates in this simple five step sequence are crystalline and simple re-crystallisation after each step allows the preparation of this exciplex fluorescence 'thermometer' molecule on a preparative scale without resort to chromatography.

Singlet excited aromatic hydrocarbons (M*) interact with amines (G) to form charge transfer intermolecular exciplexes (E*) which fluoresce:

$$M^* + G \longleftrightarrow E^*$$

The fluorescence emission of E* is red shifted relative to the emission from M*. Since the degree of exciplex formation is temperature dependent, measurement of the intensity ratio of emission from E* and M* and comparison with a previously established calibration curve allows the temperature of a system doped with the appropriate exciplex partners to be determined.[1] Optimal sensitivity and reproducibility is achieved using *intra*molecular exciplex forming dopants which

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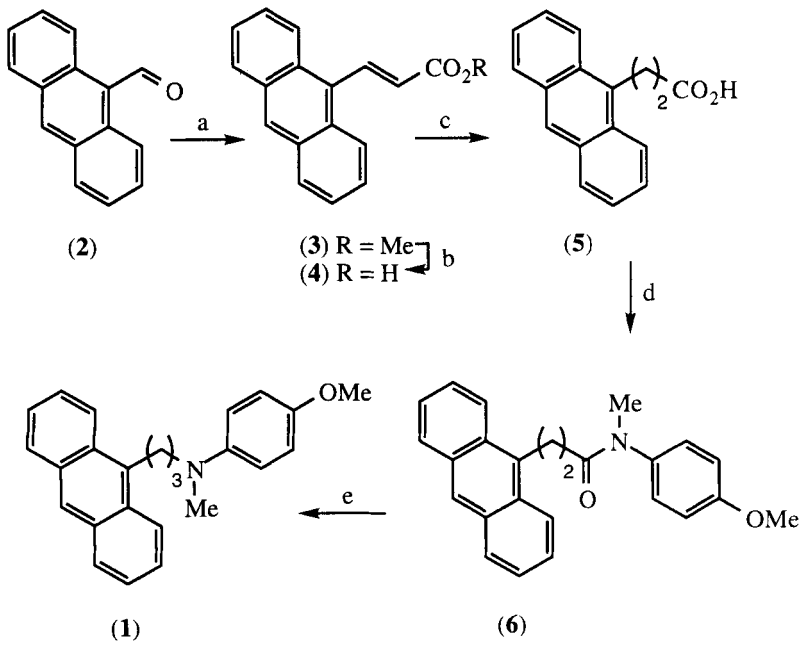
contain the aromatic electron 'acceptor' and amino 'donor' functions tethered by a three carbon alkyl chain.[2-5] Doping levels as low as 1 ppm suffice to allow accurate (±1°C) non-intrusive real-time thermometry up to 400°C in hydrocarbon sprays (e.g. automotive fuel injection systems) using laser excitation.[6-11]

We are currently exploring the application of this technique for probing the dynamics of propane jets and sprays in order to develop evaporation models which should allow us to predict dispersion patterns for industrial accidents. In connection with these studies we required gram quantities of *N*-*p*-anisyl-*N*-methyl-amino-3-(9-anthryl)-propane (**1**, Scheme I), which has been reported to display temperature dependent exciplex fluorescence between -110°C and -50°C.[12] However, the only synthesis of this compound, although requiring only three steps, was reported to proceed in just 4% overall yield from anthrone (cost ~£43 / 100g[13]).[14,15] This was too inefficient and costly to provide the quantities of product we required.

We describe here an improved route to *N*-*p*-anisyl-*N*-methyl-amino-3-(9-anthryl)-propane (**1**) from 9-anthraldehyde (**2**, cost ~£36 / 100g[13]) which requires five steps and proceeds in ~56% overall yield. No chromatography is required and all the intermediates are crystalline. This not only makes the method suited to the preparation of gram quantities of product but is advantageous even on a small scale due to the instability of these anthracene containing molecules to silica chromatography. By employing alternative anilines in the amidation-reduction sequence the preparation of analogues with modified fluorescence emission profiles should be readily accommodated. The sequence is delineated in Scheme I.

9-Anthraldehyde (**2**) is subjected to Horner-Emmons reaction with methyldimethylphosphonoacetate-sodium hydride in dimethylformamide to give



(a) $(MeO)_2P(O)CH_2CO_2Me$ (1.1 eq), NaH (1.1eq), DMF, 25°C, 30 min [**86%**]; (b) 10% KOH in EtOH, 25°C, 2 h [**95%**]; (c) H_2, 10% Pd/C (cat.), DMF, 25°C, 2 h [**90%**]; (d) i) $(COCl)_2$ (2 eq), DMF (cat.), CH_2Cl_2, 40°C, 1 h; ii) *N*-Me-*p*-anisidine (1.1 eq), Et_3N (1 eq), DMAP (0.1 eq), CH_2Cl_2, 25°C, 2 h [**91%**]; (e) $LiAlH_4$ (2 eq), THF, 25°C, 2 h [**83%**].

Scheme I

propenoate **3** (86%) essentially according to the method of Rao *et al.*[16] Propenoate **3** is saponified using 10% potassium hydroxide in ethanol and neutralised to give the corresponding acid **4** (95%) according to the method of Rockley *et al.*[17] Prior to settling for this route we explored several alternative literature preparations of ester **3** and acid **4**. Knoevenagel condensation of 9-anthraldehyde (**2**) with malonic acid[18-21] and Perkin reaction of 9-anthraldehyde (**2**) with acetic anhydride[22,21] both

afforded crude product which required multiple recrystallisations to afford a moderate yield (<50%) of pure acid **4**. Access to acid **4** via Heck type coupling between acrylic acid with 9-bromoanthracene[23] although attractive was not explored due to the high cost of the latter (~£23 / 25g[13]). The yield of ester **3** by Wittig reaction of 9-anthraldehyde (**2**) with methyl(triphenylphosphoranylidene) acetate[17,24] was compromised by the need for repeated re-crystallisation from methanol to remove traces of triphenylphosphine oxide.

Successful hydrogenation of acid **4** with molecular hydrogen (1 atm) has been reported by Davidson *et al.* using 10% Pd/C in ethanol.[20] Under these conditions we found it very difficult to prevent appreciable 'over-reduction' resulting in contamination of the product with 3-(9,10-dihydro-9-anthryl)propanoic acid.[25,19] Re-aromatisation of the crude reaction mixture by boiling with *o*-chloranil[17] or 10% Pd/C[26,21] in benzene was successful but gave moderate yields and made the process protracted and expensive. After some experimentation we found that simply changing the hydrogenation solvent to dimethylformamide completely suppressed over-reduction such that acid **5** was could be obtained in 90% yield following simple crystallisation. Alternative routes to this acid from anthrone were not explored.[27-29]

Conversion of acid **5** to amide **6** involves formation of the acid chloride using oxalyl chloride followed by treatment with *N*-methyl-*p*-anisidine and triethylamine with a catalytic amount of DMAP. Thionyl chloride[20] can also be employed in place of oxalyl chloride without significant reduction in yield. *N*-Methyl-*p*-anisidine is commercially available but expensive (cost ~£74 / 10g[13]). However, it can be readily prepared in good yield (>70%) on a large scale from *p*-anisidine (cost ~£17 /

250g[13]) according to the method of Barluenga *et al.*[30] Finally, reduction of amide **6** to *N*-*p*-anisyl-*N*-methyl-amino-3-(9-anthryl)-propane (**1**) is achieved by the use of lithium aluminium hydride in ether[20,2] employing a variant of the Steinhardt work-up[31] in which the aluminium salts are precipitated as granules by dropwise addition of water-aqueous potassium hydroxide-water successively. Direct recrystallisation of the filtrate affords the product as pale yellow prisms.

In summary, this communication describes a very convenient preparation of *N*-*p*-anisyl-*N*-methyl-amino-3-(9-anthryl)-propane (**1**) which is proto-typical of a family of *N,N*-disubstituted 1-amino-3-(9-anthryl)-propanes which display temperature dependent intramolecular charge transfer exciplex fluorescence.[15] The procedures are simple, cheap, high yielding and require no chromatography.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage. Infra red spectra were recorded as solutions in $CHCl_3$ on a Perkin-Elmer Paragon 1000 Fourier transform spectrophotometer. Only selected absorbances (ν_{max}) are reported. ^{1}H NMR spectra were recorded at 250 or 400 MHz on Bruker AM-250 or AM-400 instruments. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the residual solvent peak. Coupling constants (J) are reported to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker AM-400 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the residual solvent peak. Low resolution mass spectra (*m/z*) were recorded on a VG platform spectrometer, with only molecular ions (M^+), and major peaks being reported with intensities quoted as percentages of the base peak. Microanalysis were performed by *A.H. Jones*, Department of Chemistry, University of Sheffield, UK.

Methyl-3-(9-anthryl)propenoate (**3**)[16]. Methyl dimethylphosphonoacetate (59.3 g, 320 mmol) in dimethylformamide (100 ml) was added to a solution containing sodium hydride (7.68 g, 320 mmol) in dimethylformamide (200 ml). To this was added a solution of 9-anthraldehyde (60.0 g, 291 mmol) in dimethylformamide (100 ml). The resulting mixture was allowed to stir at room temperature for thirty minutes, quenched with water, extracted with ether, then recrystallised from methanol to give methyl-3-(9-anthryl)propenoate (**3**) as bright yellow prisms (65.8 g, 86%): m.p 114-115°C [Lit.[16] 114°C]; δ_H ($CDCl_3$, 250 MHz) 3.85 (3H, s, OCH_3), 6.37 (1H, d, *J* 15 Hz, CHCO), 7.45 (4H, m, ArH), 7.94 (2H, m, ArH), 8.18 (2H, m, ArH), 8.39 (1H, s, ArH), 8.58 (1H, d, *J* 15 Hz, ArC*H*=CH).

3-(9-Anthryl)propenoic acid (**4**)[17]. Methyl ester **3** (5.0 g, 19 mmol) was dissolved in a 10% ethanolic solution of potassium hydroxide (300 ml) and the resulting solution stirred for two hours at room temperature. Concentration *in vacuo*, addition of hydrochloric acid (2 N, 400 ml) and extraction with ethyl acetate (5x300ml) followed by evaporation and recrystallisation from ethyl acetate gave 3-(9-anthryl)propenoic acid (**4**) as fine yellow needles (4.5 g, 95%): m.p. 245-246°C [Lit.[17] 244-245°C (EtOH)]; δ_H ($CDCl_3$, 250 MHz), 6.5 (1H, d, *J* 15 Hz, CHCO), 7.52 (4H, m, ArH), 8.03 (2H, m, ArH), 8.23 (2H, m, ArH), 8.48 (1H, s, ArH), 8.84 (1H, d, *J* 15 Hz, ArC*H*=CH).

3-(9-Anthryl)propanoic acid (**5**)[17]. 3-(9-Anthryl)propenoic acid (**4**) (2.0 g, 8.1 mmol) was hydrogenated at atmospheric pressure over 10% palladium on charcoal (400 mg) in dry dimethylformamide (20 ml) for two hours at room temperature. The solution was filtered through Celite to remove the catalyst and the

Celite washed through with more dry dimethylformamide (2x20 ml). The filtrate was concentrated *in vacuo* and the residue recrystallised from absolute ethanol to give 3-(9-anthryl)propanoic acid (**5**) as pale yellow prisms (1.81 g, 90%): m.p. 193-194°C [Lit.[27] 194-195°C (AcOH)]; δ_H ($CDCl_3$, 250 MHz), 2.80 (2H, m, CH_2), 3.94 (2H, m, CH_2), 7.46 (4H, m, ArH), 7.96 (2H, d, *J* 8 Hz, ArH), 8.19 (2H, d, *J* 8 Hz, ArH), 8.33 (1H, s, ArH).

***N*-*p*-Anisyl-*N*-methyl-3-(9-anthryl)propanamide** (**6**). To 3-(9-anthryl)propanoic acid (**5**) (0.50 g, 2.0 mmol) in dichloromethane (10 ml) was added oxalyl chloride (352 µl, 4.0 mmol). The mixture was refluxed for 1 hour then evaporated to dryness. To this crude 3-(9-anthryl)propanoyl chloride was added *N*-methyl-*p*-anisidine (305 mg, 2.2 mmol) in dichloromethane (10 ml). Dimethylaminopyridine (25 mg, 0.20 mmol) was added and the mixture was stirred under argon for 2 hours. The solution was quenched with 2N H_2SO_4 (10 ml) and extracted with dichloromethane (3x10 ml) and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo*. The pale brown solid residue was recrystallised from EtOAc:40-60 petrol to afford *N*-*p*-anisyl-*N*-methyl-3-(9-anthryl)propanamide (**6**) as pale yellow prisms (0.670 g, 91%): m.p. 156.5-157.5°C; Found *m/z* (EI^+) M^+ 369.172775, $C_{25}H_{23}NO_2$ requires M^+ 369.172879; Found: C 81.45, H 6.24, N 3.72%, $C_{25}H_{23}NO_2$ requires C 81.27, H 6.27, N 3.79%; δ_H ($CDCl_3$, 400 MHz), 2.59 (2H, m, CH_2), 3.27 (3H, s, NCH_3), 3.71 (3H, s, OCH_3), 3.88 (2H, m, CH_2), 6.72 (2H, d, *J* 9 Hz, ArH), 6.87 (2H, d, *J* 9 Hz, ArH), 7.42 (4H, m, ArH), 7.94 (2H, m, ArH), 8.02 (2H, m, ArH), 8.28 (1H, s, ArH); δ_C ($CDCl_3$, 100 MHz), 24.1 (t), 35.1 (t), 37.4 (q), 55.2 (q), 114.6 (2d), 123.9 (2d), 124.7 (2d), 125.4 (2d), 125.8 (d), 128.1 (2d), 128.9 (2d),

129.3 (2s), 131.3 (2s), 133.0 (s), 136.4 (s), 158.6 (s), 172.7 (s); *m/z* (EI^+), 369 (90%), 231 (100), 202 (68), 191 (72), 149 (46), 137 (59).

***N*-*p*-Anisyl-*N*-methyl-amino-3-(9-anthryl)-propane (1)**[15]. To a solution of *N*-*p*-anisyl-*N*-methyl-3-(9-anthryl)propanamide (**6**) (0.50 g, 1.4 mmol) in dry diethyl ether (10 ml) was added lithium aluminium hydride (106 mg, 2.8 mmol). The mixture was left to stir for 2 hours at room temperature prior to cautious successive dropwise addition of water (106 µl), 2N NaOH (212 µl) and water (106 µl). After stirring for 10 min the granular aluminium salts were filtered off, the filtrate dried (Na_2SO_4), concentrated *in vacuo*, and the residue recrystallised from 40-60 petrol to give *N*-*p*-anisyl-*N*-methyl-amino-3-(9-anthryl)-propane (**1**) as pale yellow prisms (0.399 g, 83%) m.p. 124-125°C [Lit.[15] 121°C (60-70 Petrol)]; Found *m/z* (EI^+) M^+ 355.193585, $C_{25}H_{25}NO$ requires M^+ 355.193615; Found: C 84.59, H 7.02, N 3.81%, $C_{25}H_{25}NO$ requires C 84.47, H 7.09, N 3.94%; δ_H ($CDCl_3$, 400 MHz), 2.07 (2H, m, CH_2), 2.92 (3H, s, NCH_3), 3.47 (2H, t, *J* 7 Hz, CH_2), 3.65 (2H, t, *J* 7 Hz, CH_2), 3.77 (3H, s, OCH_3), 6.78 (2H, d, *J* 9 Hz, ArH), 6.85 (2H, d, *J* 9 Hz, ArH), 7.47 (4H, m, ArH), 8.00 (2H, m, ArH), 8.20 (2H, m, ArH), 8.33 (1H, s, ArH); δ_C ($CDCl_3$, 100 MHz), 25.5 (t), 28.4 (t). 39.6 (q), 54.2 (t), 55.8 (q), 114.7 (2d), 115.2 (2d), 124.2 (2d), 124.8 (2d), 125.5 (2d), 125.7 (d), 129.2 (2d), 129.5 (2s), 131.6 (2s), 134.4 (s), 144.4 (s), 151.8 (s); *m/z* (EI^+), 355 (100%), 191 (38), 176 (82), 150 (88).

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