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Functionalisation of the hinge region in receptor molecules for explosive detection

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Abstract—The functionalisation of the hinge region in a molecular tweezer molecule showing a strong binding to explosives is presented. Two versatile functional groups are introduced, a carboxylic acid and a bromine atom.

1. Introduction

Recently, a molecular tweezer showing strong binding of electron deficient planar aromatic molecules such as typical explosives (e.g. trinitrotoluene) was reported.[1] The molecular tweezer is composed of two large electron-rich aromatic plates attached together by a preorganised hinge region based on 2,6-diphenylpyridine. The 1*H*-phenanthro[9,10-*d*]imidazole system is a supramolecular building block that is easily synthesised from phenanthrenequinone, an aromatic aldehyde and a source of ammonia that besides its reported use in explosive receptors has been successfully employed as the chromophore in stable superradiant laser dyes[2] and has been used as the pumping chromophore in fluorinated supramolecular assemblies that exhibit twisted intramolecular charge transfer (TICT).[3] The use of molecular tweezer molecules in sensor systems sensitive to explosives requires a means for the attachment of the receptor molecules onto surfaces, larger assemblies or polymers. The best strategy for attachment employs functionalisation of the hinge region as this is farthest away from the pocket where the binding of solutes takes place. An attachment strategy involving the 1*H*-phenanthro[9,10-*d*]imidazole moieties would introduce two complications: (1) a larger likelihood of a negative influence on the binding constant and, (2) the problem of making an unsymmetrical tweezer molecule. Attachment to the hinge region avoids both of these potential problems.

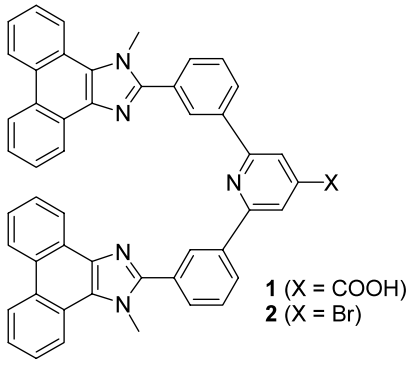
Here I wish to present experimental procedures allowing for the derivatisation of the hinge region in molecular tweezers by a bromine or a carboxylic acid group as shown in Scheme 1.

2. Experimental

Melting points are uncorrected. NMR spectra were run at 300 K unless otherwise stated. In the ^{13}C NMR spectrum of compound **2** two signals are missing. This is ascribed to accidental isochrony.

2.1. 2,6-Bis(3-(1-methyl-phenanthro[9,10-*d*]imidazol-2-yl)-phenyl)-4-carboxypyridine 1

4-Ethyloxycarbonyl-2,6-dibromopyridine (3.1 g, 10 mmol), compound **4** (10 g, excess), water (250 mL), toluene (500 mL), Na_2CO_3 (25 g, excess), $(Ph_3P)_2PdCl_2$



Scheme 1.

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(0.5 g, catalytic) were mixed under argon and heated to reflux. Initially the mixture acquired a red colour and then a thick brown mass formed. After 16 h the mixture was a thick slurry and $(Ph_3P)_2PdCl_2$ (0.5 g) and an additional portion of compound **4** (3 g) were added and reflux continued. After reflux for a total of 48 h the mixture was filtered while hot (very time consuming). The toluene phase contained mostly the homo-coupled boronic acid. The grey paste was stirred in a 1:1 mixture of water and diethylether (1 L) and filtered (time consuming). The fine paste like filter-cake was boiled in acetic acid (500 mL) then filtered while boiling. The combined filtrate was poured into water (2 L). The colourless precipitate was filtered and boiled in methanol (500 mL), then filtered and dried. This gave 1.04 g (14%) of **1** as a colourless solid: mp 250–252°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.90–8.70 (m, 6H), 8.60–8.4 (m, 2H), 8.35–8.2 (m, 6H), 8.00–7.90 (m, 2H), 7.70–7.40 (m, 10H), 4.24 (s, 6H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 166.1, 156.1, 151.6, 141.0, 138.2, 136.5, 130.7, 130.6, 129.2, 128.1, 127.9, 127.5, 127.4, 127.2, 126.9, 126.7, 125.2, 124.8, 124.1, 123.3, 123.0, 121.73, 121.72, 120.9, 118.2, 35.9; MALDIFTMS m/z 735.20 (M^+, $C_{50}H_{33}N_5O_2$ requires 735.26); Anal. calcd for $C_{50}H_{33}N_5O_2 2H_2O$: C, 77.80; H, 4.83; N, 9.07. Found: C, 77.54; H, 4.32; N, 8.75.

2.2. 2,6-Bis(3-(1-methyl-phenanthro[9,10-*d*]imidazol-2-yl)-phenyl)-4-bromopyridine 2

Compound **6** (7.52 g, 10 mmol) was suspended in acetone (500 mL) and acetyl bromide (15 mL, excess) was added. The mixture was refluxed for 4 h. Initially the colour of the suspension was bright yellow but upon addition of acetyl bromide the colour quickly became pale yellow. At the end of the reaction the colour was brown. The mixture was cooled and the intermediate product **7** was filtered, washed with acetone, ether and dichloromethane. This gave 9.12 g (87%) of a light yellow fine powdery product that was concluded to be the dihydrobromide with one solvent dichloromethane molecule as indicated by elemental analysis. The material was only soluble in DMSO for NMR purposes but was found to decompose in that solvent: mp>271–273°C; Anal. calcd for $C_{51}H_{35}BrN_6O_4 2HBr \cdot CH_2Cl_2$: C, 55.44; H, 3.85; N, 7.46. Found: C, 55.14; H, 3.50; N, 7.77. The product was used directly in the following reaction. Compound **7** (9.12 g, 8.74 mmol) was suspended in chloroform (600 mL). PBr_3 (12 mL, excess) was added and the suspension was heated to reflux under Ar. After 1 h the mixture became lighter in colour and milky. Reflux was continued for 24 h. Towards the end the mixture was light yellow and milky. After cooling the mixture was poured into water and a thick precipitate formed that was filtered (very time consuming). The wet product was dissolved in pyridine and evaporated to dryness. The solid was boiled in water and filtered, washed with ethanol and ether and then dried. This gave crude **2** as a colourless yellow compound 5.3 g (69%) that was of a sufficient purity for further synthetic work. An analytical sample was obtained by dry column chromatography on silica using an ethyl acetate/heptane gradient starting with pure heptane and gradually increasing the ethyl acetate content in 5% steps: mp 175–177°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.70–8.60 (m, 6H), 8.54 (d, ^3J (H, H) = 8 Hz, 2H), 8.30–8.20 (m, 4H), 7.83 (d, ^3J (H, H) = 8 Hz, 2H), 7.69 (t, ^3J (H, H) = 8 Hz, 2H), 7.58–7.38 (m, 8H), 7.31 (s, 2H), 4.12 (s, 6H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 157.0, 155.9, 152.4, 140.5, 137.0, 130.9, 130.2, 129.4, 128.6, 128.4, 127.9, 127.7, 127.5, 127.2, 127.1, 125.7, 125.2, 125.6, 123.8, 123.5, 122.2, 121.3, 36.3; MALDIFTMS (DHB) m/z 770.22 ($M+H^+$, $C_{49}H_{33}N_5Br$ requires 770.19); Anal. calcd for $C_{49}H_{32}N_5Br$: C, 76.36; H, 4.18; N, 9.09. Found: C, 76.24; H, 4.31; N, 8.79.

2.3. 4-Nitro-2,6-bis(3-(1-methyl-phenanthro[9,10-*d*]-imidazol-2-yl)phenyl)pyridine-*N*-oxide (6)

Compound **5** (9 g, 30 mmol), compound **4** (24 g, 61.7 mmol), Na_2CO_3 (36 g, excess), water (300 mL), toluene (450 mL) were mixed in a 1 L conical flask and degassed with argon. $(Ph_3P)_2PdCl_2$ (0.75 g, catalytic) was added and the yellow slurry heated to reflux. After 24 h of reflux a thick creamy orange emulsion had formed. The mixture was cooled, filtered and the product washed with water (200 mL), ethanol (200 mL), ether (200 mL), CCl_4 (200 mL) and finally dried. This gave 19.2 g (85%) of **6** as a bright yellow powder: mp 247–250°C; ^{1}H NMR (250 MHz, 400 K, DMSO-d_6) δ 8.80 (d, ^3J (H, H) = 8 Hz, 2H), 8.72 (d, ^3J (H, H) = 7 Hz, 2H), 8.61 (d, ^3J (H, H) = 8 Hz, 2H), 8.52 (d, ^3J (H, H) = 7 Hz, 2H), 8.40–8.30 (m, 4H), 8.00–7.95 (m, 4H), 7.70–7.20 (m, 10H), 4.30 (s, 6H); ^{13}C NMR (63 MHz, 400K, DMSO-d_6) δ 150.9, 136.4, 131.6, 130.3, 129.95, 129.90, 129.4, 127.9, 127.8, 127.1, 126.9, 126.5, 126.3, 126.1, 124.6, 124.5, 124.2, 124.1, 123.5, 122.7, 122.6, 121.2, 120.4, 120.3, 35.1; MALDIFTMS (DHB) m/z 752.17 (M^+, $C_{49}H_{32}N_6O_3$ requires 752.25); Anal. calcd for $C_{49}H_{32}N_6O_3CCl_4$: C, 66.24; H, 3.56; N, 9.27. Found: C, 65.99; H, 3.68; N, 9.41.

2.4. 4-(*N*-Benzylamino)benzenethiol hydrochloride 8

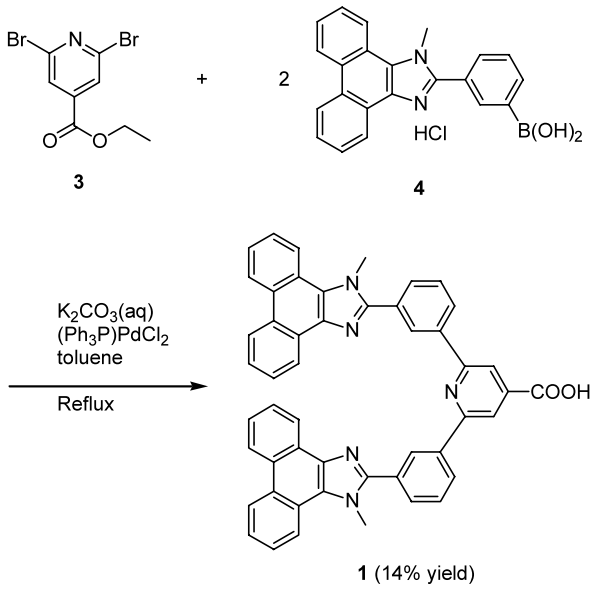
4-Mercaptoaniline (25 g, technical grade 90%, 0.18 mol) was dissolved in EtOH (99%) (400 mL) under argon and stirred while benzaldehyde (21.6 g) was added followed by acetic acid (1 mL) was added. After 1 min a light yellow precipitate formed. After stirring for 10 min the precipitate was filtered and dissolved in THF (400 mL). Acetic acid (50 mL) was added followed by careful addition of $NaBH_4$ (10 g, excess) with cooling in an ice bath. After the addition, the mixture was stirred for 30 min. Water was added carefully and the mixture evaporated to give an oil which was stirred with HCl (aq.) 35% (100 mL). A yellow precipitate formed which was filtered and washed with water, ethanol, petroleum and finally dried. The product was soluble in DMSO-d_6 but the NMR experiment revealed that the product reacts with atmospheric oxygen (or DMSO) to give the disulphide under the conditions of the NMR experiment. This gave 45 g (99%) of **8** as a light yellow powder: mp 198–200°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.4 (bs, 2H), 7.50–7.20 (m, 9H), 5.81 (bs, 1H), 4.45 (s, 2H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 142.9,

135.8, 131.3, 128.6, 128.2, 127.9, 127.6, 118.1, 49.5; MALDIFTMS m/z 215.25 (M^+, $C_{13}H_{13}NS$ requires 215.07); Anal. calcd for $C_{13}H_{14}ClNS$: C, 62.02; H, 5.60; N, 5.56. Found: C, 61.88; H, 5.55; N, 5.43.

2.5. 4-(4-Benzylaminophenylthio)-2,6-bis(3-(1-methylphenanthro[9,10-*d*]imidazol-2-yl)phenyl)pyridine 9

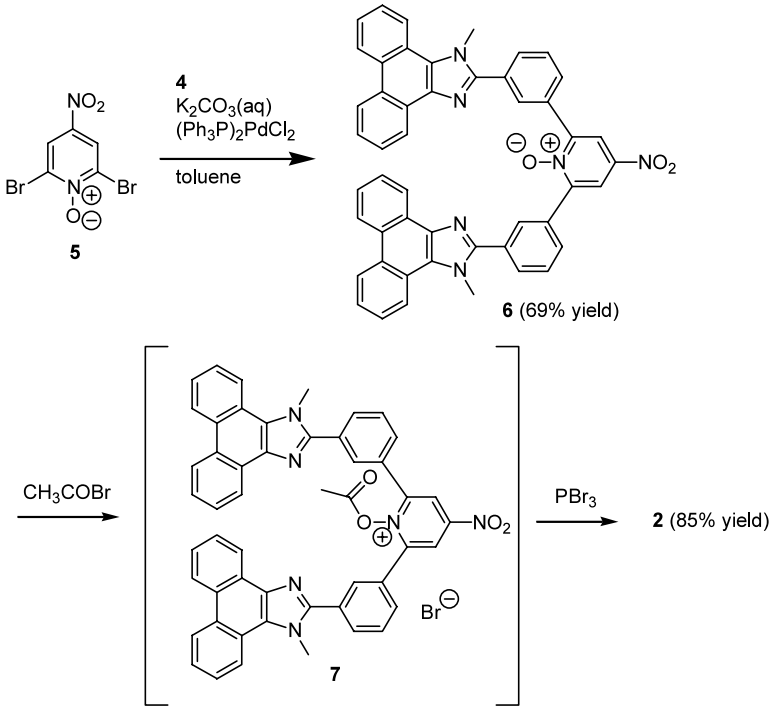
Compound **2** (1.54 g, 2 mmol), compound **8** (0.5 g, 2 mmol), K_2CO_3 (1 g, excess) were mixed in dry DMF (20 ml) under argon. The mixture was refluxed for 1 h, then poured into water and filtered, washed with ether and dissolved in chloroform:THF/3:1, dried with a little $MgSO_4$ and passed through a large funnel with silica (10 cm∅×5 cm) in the same solvent mixture. The filtrate was evaporated and dissolved in chloroform (25 mL) and added to ether (200 mL). The product 1.32 g (73%) precipitated as a light tan solid: mp 212–215°C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.80–6.80 (m, 36H), 4.27 (s, 2H), 4.20 (s, 6H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 154.9, 154.0, 151.4, 149.9, 138.9, 138.5, 136.4, 136.2, 133.0, 130.5, 129.9, 128.6, 127.9, 127.7, 127.3, 127.1, 127.0, 126.6, 126.57, 126.51, 126.3, 126.1, 124.7, 124.3, 123.7, 122.8, 121.4, 120.5, 114.9, 113.2, 112.4, 111.8, 46.0, 35.3; MALDIFTMS m/z 904.23 (M^+, $C_{62}H_{44}N_6S$ requires 904.33); Anal. calcd for $C_{62}H_{44}N_6S{\cdot}H_2O$: C, 80.67; H, 5.02; N, 9.10. Found: C, 80.50; H, 4.71; N, 9.15.

The efficient synthetic strategy was based on the employment of suitable 2,6-dibromopyridine derivatives functionalised in the 4-position. In the case of a carboxylic acid functionality the synthetic procedure followed a standard Suzuki coupling reaction between

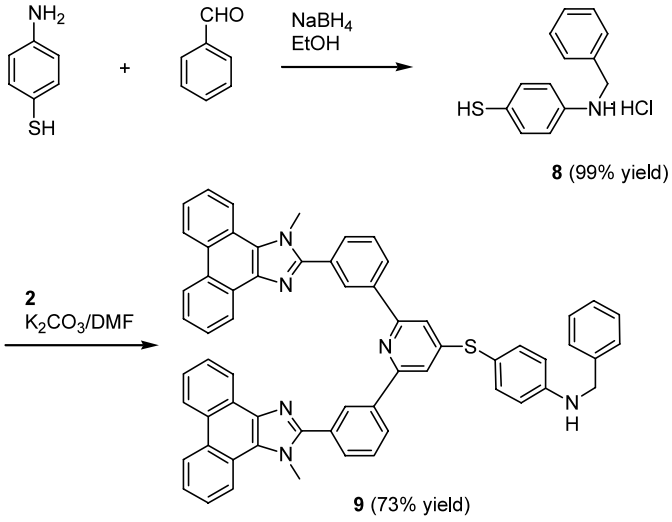


Scheme 2.

2,6-dibromo-4-ethyloxycarbonylpyridine **3** and 3-(1-methylphenanthro[9,10-*d*]imidazol-2-yl)-phenylboronic acid hydrochloride **4**. Compound **4** was obtained as described in reference 1 and compound **3** was easily obtained by treatment of citrazinic acid with phosphorous oxybromide as described by Levelt et al.[4] followed by esterification with ethanol/conc. H_2SO_4 as described by Ulrich et al.[5] The desired functionalised compound **1** was worked-up directly from the reaction mixture as shown in Scheme 2. The use of a two phase system with toluene as the organic phase and



Scheme 3.



Scheme 4.

potassium carbonate in the aqueous phase gave rise to in situ saponification of the acid making the isolation of a pure product free of homo-coupled by-products possible, albeit in low yield.

The introduction of a bromine atom however proved to be more difficult since the Suzuki coupling took place at all positions when using 2,4,6-tribromopyridine. Instead, the route to derivatisation of the pyridine system in the 4-position developed firstly by Evans et al.[6] and later Vögtle et al.[7] was employed thus allowing for the introduction of the bromine atom after the Suzuki coupling took place. The procedure is shown in Scheme 3. The reaction between 2,6-dibromo-4-nitropyridine-*N*-oxide proceeded in good yield. The final bromination reaction was carried out by reaction with acetyl bromide followed by reaction with phosphorus tribromide. The reaction with acetyl bromide leads to acylation at the oxygen atom of the *N*-oxide and it was possible to isolate the bromide salt **7**. Compound **7** was, however, difficult to analyse as it decomposed readily in DMSO-d_6 during the NMR experiment. DMSO was found to be the only readily available NMR-solvent that was able to dissolve **7**. The decomposition in DMSO was confirmed by making the simple *O*-acetyl derivative of compound **5** which also decomposed in DMSO-d_6. In principle the decomposition of compound **7** should give compound **2**[7] but the product was always contaminated with a large proportion of the 4-nitro derivative. Treatment with phosphorus tribromide solved this problem resulting in a very small degree of contamination with by-products possesing a nitro group in the 4-position.

Further reaction on the brominated tweezer compound was found to be possible using good nucleophiles such as sulphide. In Scheme 4 an example of a reaction of *N*-benzylated 4-mercaptoaniline **8** with compound **2** is shown. The basic form of compound **8** was found to form the disulphide on standing and was most easily stored as the hydrochloride salt. Compound **8** was also found to form the disulphide under the conditions of the NMR experiment. The reaction between **8** and **2** proceeded smoothly giving compound **9** which has the hinge region functionalised with a spacer suited for attachment to acid chlorides, carbamoyl chlorides or chloroformates.

In summary, the tweezer system is very stable towards various chemical reactions involving both mild and harsh conditions. This allowed for the demonstration of preparative scale synthesis of molecular tweezer molecules with functionality in the hinge region.

Acknowledgements

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