An Improved Synthesis and Structural Characterisation of 2-(4-Acetylthiophenylethynyl)-4-nitro-5-phenylethynylaniline: The Molecule Showing High Negative Differential Resistance (NDR)

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Abstract: 2-(4-Acetylthiophenylethynyl)-4-nitro-5-phenyl-ethynylaniline (**11**) has been synthesised by an improved route, which has many advantages over the literature procedure. A key intermediate is 2-ethynyl-4-nitro-5-phenylethynylaniline (**6**) which is obtained from 2,5-dibromoacetanilide (5 steps, 68% overall yield). Reaction of **6** with 1-acetylthio-4-iodobenzene under Sonogashira coupling conditions affords **11** (56%). Compound **11** is characterised by CHN analysis, mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. The crystal structures of 2-bromo-4-nitro-5-phenylethynylaniline (**4**), 2-(3-hydroxy-3-methylbutynyl)-4-nitro-5-phenylethynylaniline (**5**) and 2-[(4-methoxybenzylthio)phenylethynyl]-4-nitro-5-phenylethynylaniline (**15**), have been determined, by which the regiochemical structure of **11** is also proved. The intramolecular contacts O(1)···C(7) of 2.692(2) Å in **4** and 2.677(2) Å in **15** are considerably shorter than the standard van der Waals O···C contact of 3.24 Å.

Key words: 2-(4-acetylthiophenylethynyl)-4-nitro-5-phenylethynylaniline, negative differential resistance, molecular wires, Sonogashira coupling

2-(4-Acetylthiophenylethynyl)-4-nitro-5-phenylethynylaniline (**11**) is a promising candidate for molecular electronic devices which could perform logic and memory functions, due to the discovery in 1999 of its unusually high negative differential resistance (NDR) in self-assembled monolayers.[1] The synthetic details and structural characterisation of this particularly interesting molecule were reported by Tour and co-workers in 2001.[2] In their synthesis, 2,5-dibromoacetanilide (**1**) was nitrated to afford 2,5-dibromo-4-nitroacetanilide (**2**) (Scheme 1). The cross-coupling of **2** with phenylacetylene yielded 2-bromo-4-nitro-5-phenylethynylacetanilide, which was then deacetylated to afford the key intermediate, 2-bromo-4-nitro-5-phenylethynylaniline (**4**). The cross-coupling of **4** with 4-acetylthiophenylacetylene afforded the final product **11**.

In seeking to prepare a sample of compound **11** with high purity, we recognised that the following problems in the reported procedure[2] had to be overcome.

1) The nitration of **1** was reported to be explosive, and therefore, the nitro derivative **2** was not isolated and purified prior to the subsequent reactions.[3]

2) The regioselectivity of the mono cross-coupling of **2** with phenylacetylene was not proved, but assumed. As a result, the regiochemical structure of **11** was also not rigorously proved. This is because phenylacetylene could replace either of the bromine atoms in molecule **2** leading to two different regioisomers, although the Br on C-5 is expected to be more reactive in Sonogashira coupling reactions.

3) The synthesis of the other key building block, i.e., 4-acetylthiophenylacetylene proved to be problematic in our laboratory. We were not able to reproduce the lithiation of 1,4-diiodobenzene as reported[4] although a modification of this procedure has been published during the preparation of this manuscript.[5] In addition, the melting point and purity of compound **11** (i.e. C,H,N analysis) remained unreported.[1,2,6]

In this paper, we report a much improved procedure for the preparation of compound **11**. Our improvements and modifications are as follows.

1) We optimised the reaction conditions for the nitration of **1** (Scheme 1) and have isolated the nitro derivative **2** in >20 g batches (86% yield after recrystallisation) without any explosion. A likely explanation for the explosions encountered[3] is that the reaction temperature was not precisely controlled, leading to explosive multi-nitrated side-products. A very slow addition of nitric acid at low temperature (an external temperature of –10 to –15 °C was needed to maintain an internal temperature of –3 to –5 °C) during the addition is particularly important.

2) Instead of directly coupling **2** with phenylacetylene, compound **2** was deacetylated to afford **3** prior to the coupling reaction. We reasoned that the increased electron-donating ability of the amino group should enhance the reactivity difference of the bromine atoms of **3** towards Sonogashira coupling, leading to cleaner formation of **4**, with a smaller proportion of the regioisomer arising from displacement of the Br at C-2. We were unable to reproduce the reported deacetylation of **2** using 1 M HCl[7] possibly because the structure claimed to be compound **2** had been incorrectly assigned: (it was not fully characterised

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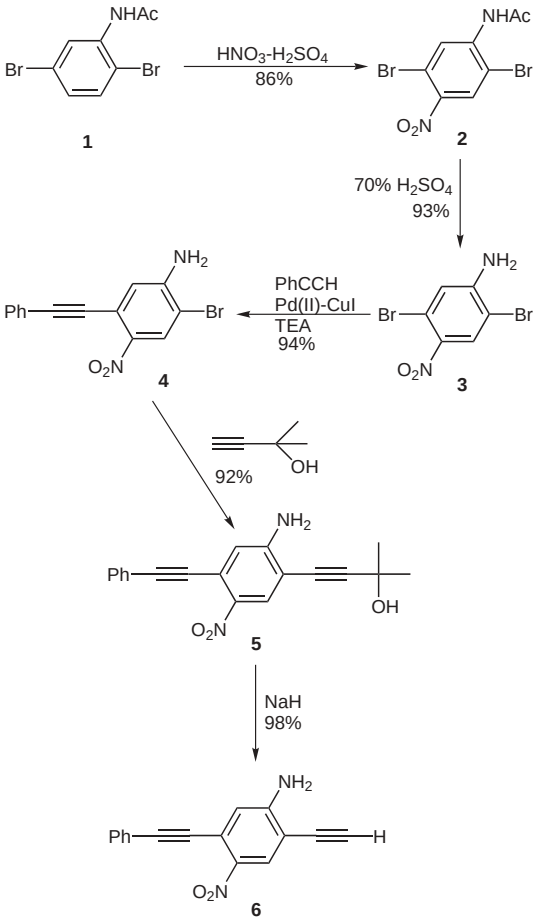


Scheme 1

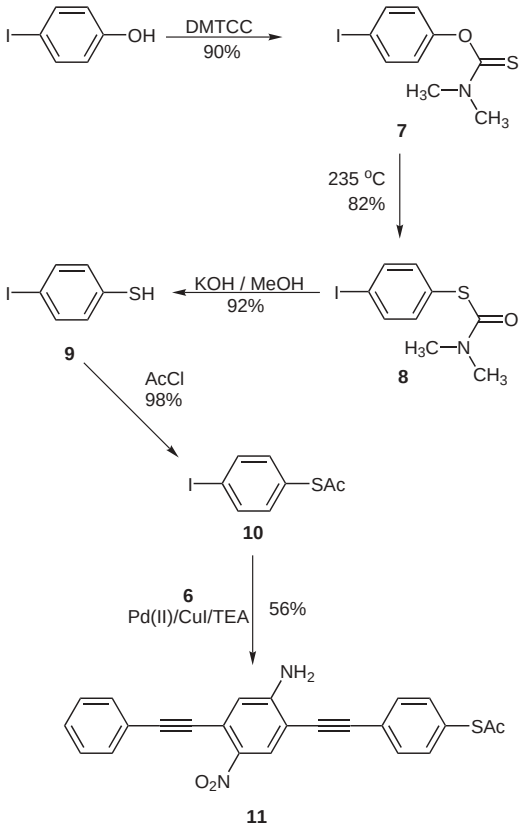
and had mp 204–205 °C, whereas our pure sample of **2** had mp 183.9–185.3 °C). We found that the reaction of **2** in 70% sulfuric acid gave **3** in 93% yield. In contrast to the report,[7] our product was insoluble in 1 M HCl even after sonication and heating.

3) The mono cross-coupled intermediate **4** was obtained in 94% yield and its structure was unambiguously established by X-ray diffraction in addition to its routine analysis. Importantly, the crystal structures of **4** and **5** proved that the phenylethynyl functionality was attached at C-5. The eventual regiochemistry of **11**, which is derived from **4**, is, therefore, ascertained beyond doubt.

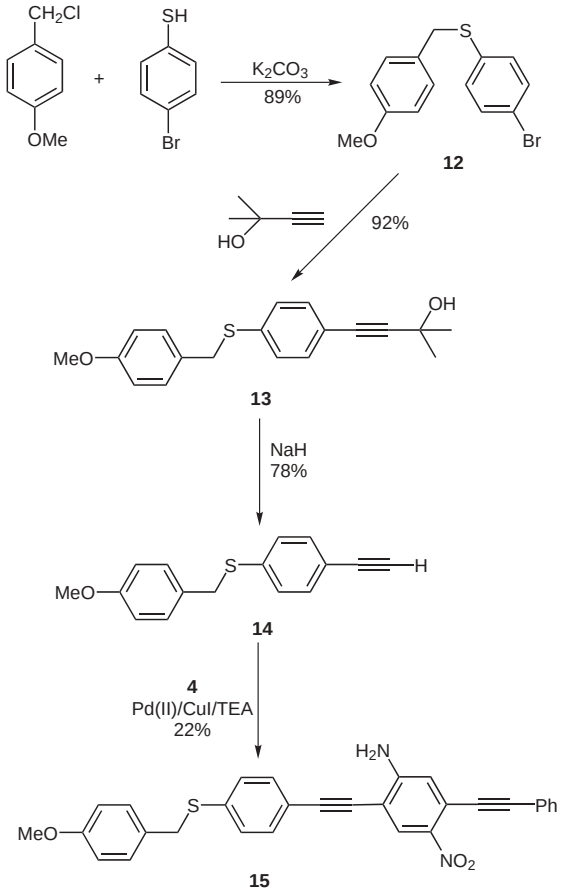
4) A different route has been used to prepare **11**. We synthesised first the terminal alkyne derivative **6**, then cross-coupled it with 1-acetylthio-4-iodobenzene (**10**) (Scheme 2).

This route is preferable to Tour's procedure[1,2] for several reasons. Firstly, it enables the use of a large excess of terminal alkyne, i.e. 2-methyl-3-butyn-2-ol, to overcome the low reactivity of **4** (which is an aromatic bromide) towards Sonogashira coupling. Secondly, the coupled product **5** can be easily purified by column chromatography due to its high polarity caused by the hydroxy group. Thirdly, in the last step of the sequence to afford **11**, coupling takes place between the terminal alkyne **6** and the more reactive aromatic iodide **10**. Another reason which persuaded us to avoid the reaction of **4** with 4-acetylthiophenylacetylene was that during the attempted synthesis of **11**, by deprotection of compound **15** followed by acetylation of the resulting thiolate (Scheme 3), the self-coupling of the terminal acetylene **14** was the dominant reaction. As documented, the self-coupling of terminal acetylenes is common when unreactive aromatic bromides[8a,b] or nonaromatic halides[8c] are used under Sonogashira reaction conditions. Therefore, the cross-coupling of **14** with compound **4** to yield **15** was inefficient. This may suggest that coupling between **4** and 4-acetylthiophenylacetylene is similarly inefficient. A side benefit from the route we abandoned was that compound **15** was more crystalline than **11** which allowed us to obtain a single crystal X-ray structure. The crystal structure of **15** (as with **4** and **5**) indirectly confirmed the regiochemical structure of **11**.

Another significant practical improvement in Scheme 2 is that instead of the tricky monolithiation of 1,4-diiodobenzene with *tert*-butyllithium,[4] we developed a more convenient and reliable way to synthesise 1-acetylthio-4-iodobenzene (**10**). 4-Iodophenol reacted with *N*,*N*-dimethylthiocarbamoyl chloride (DMTCC) to afford the *O*-ester **7** in 90% yield. Using a Kugelrohr oven, the Newman–Karnes conversion[9] of **7** to the *S*-ester **8** proceeded in good yield. The subsequent hydrolysis and acetylation leading to analytically pure **10** are straightforward reactions. (The overall yield of **10** from 4-iodophenol was 67%).



Scheme 2



Scheme 3

These new routes to both reagents **6** and **10** have allowed us to repeat the synthesis many times and have made available sufficient quantity of compound **11** for careful purification, structural characterisation and physical studies. We have been unable to prepare a single crystal of **11**. Solid samples of **11** were shelf-stable at ambient conditions for weeks. However, solutions in THF stored in sealed vials decomposed within a few days on the bench under room light, as shown by HPLC analysis and darkening of the solutions.

The X-ray molecular structures of **4** and **15** are shown in Figures 1 and 2, respectively. In both molecules, the 4-nitro-5-phenylethynylaniline moiety adopts a near-planar conformation: the essentially flat amino group, the nitro group and benzene ring *ii* are inclined to ring *i* by 2.7(13), 0.3(1) and 4.0(1)°, respectively, in **4**, and by 4.7(17), 4.6(1) and 5.3(1)° in **15**. The resulting intramolecular contacts O(1)···C(7) of 2.692(2) Å in **4** and 2.677(2) Å in **15** are considerably shorter than the standard van der Waals O···C contact of 3.24 Å.[10] This interaction must be responsible for a decrease of the C(4)–C(7)–C(8) angle to 171.6(2)° (**4**) and 171.7(2)° (**15**). The bond distances C–NH_2 [1.351(2) Å] and C–NO_2 [1.446(2) Å] are identical in **4** and **15**, and practically coincide with those in *p*-nitroaniline [1.355(2) and 1.433(2) Å, respectively].[11] In the latter, the benzene ring geometry is substantially quinoidal, which is not pronounced in **4** and **15**, probably obscured by the effects of other substituents. The remaining part of molecule **15** is not planar, with the dihedral angle of 25.7(1)° between benzene rings *i* and *iii*, and 84.1(1)° between rings *iii* and *iv*. In both structures, one H atom of the amino group participates in an intermolecular hydrogen bond [N(2)–H···O(2) in **4**; N(2)–H···S in **15**]. These bonds link molecules, related by a glide plane *c* (in **4**) or by an *a*–*b* translation (in **15**) into an infinite chain. The other amino H atom forms a short intramolecular contact with the substituent at C(1), which can be interpreted as a N–H···Br or N–H··· π(C⎪C) hydrogen bond, albeit a forced one.

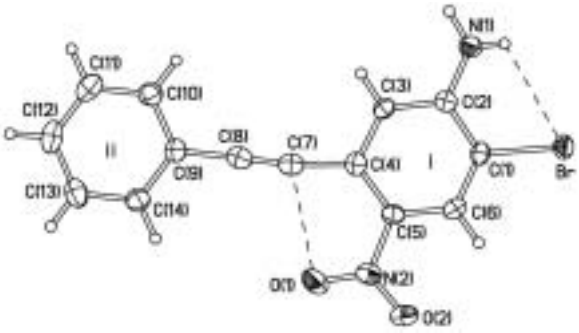


Figure 1 Molecular structure of **4**, showing 50% displacement ellipsoids.

In summary, this paper describes a new synthesis of the title compound **11** which is an important molecule in contemporary molecular electronic device studies.[1–3,6] This route offers significant improvements over the literature procedure[2] and provides efficient access to versatile phe-

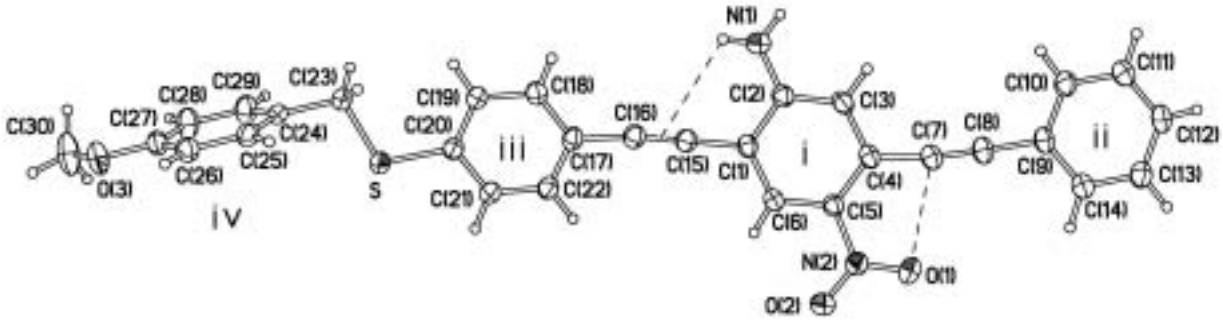


Figure 2 Molecular structure of **15**.

nylene-ethynylene derivatives, which are suitable building blocks for the construction of a range of functional molecular wires of well-defined conjugation lengths.[12]

2,5-Dibromoacetanilide was prepared as described[3] and recrystallised from EtOH as white crystals; mp 176.8–178.3 °C (Lit.[3] mp 170–171 °C). THF and Et_3N were dried over sodium metal and freshly distilled before use. Petroleum ether used had bp 40–60 °C. Flasks used to carry out Sonogashira coupling reactions were flame-dried and coupling reactions were all protected with an argon atmosphere. Dichlorobis(triphenylphosphine)palladium (II) was prepared by the reported method.[13] CuI was used as purchased from Avocado (98%+ grade). The Kugelrohr apparatus used for the preparation of **8** was a Büchi B-580 glass oven and the temperatures were direct readings of the display without calibration. Most of the ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-300 spectrometer operating at 299.91 MHz for ^1H and 75.41 MHz for ^{13}C unless indicated otherwise. In those cases, 400 MHz and 200 MHz refer to Varian VXR 400s and Varian Mercury 200 spectrometers, respectively. Chemical shifts are quoted downfield from TMS. Electron Impact (EI) mass spectra were recorded on a Micromass AutoSpec spectrometer operating at 70 eV. Elemental analyses were obtained on an Exeter Analytical Inc. CE-440 elemental analyser. Melting points were measured in open-end capillaries using a Stuart Scientific SMP3 melting point apparatus. The temperatures at the melting points were ramped at 2.5 °C/min and are uncorrected.

Crystallographic Studies

X-ray diffraction experiments (see Table 1) were carried out on a SMART 3-circle diffractometer with a 6K CCD area detector, using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. Full sphere of reciprocal space to $2\theta = 60^o$ was covered by 4 sets of 0.3° ω scans, each set with different φ and/or 2θ angles. The intensities were corrected for absorption by numerical integration based on real crystal shape. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL software.[14] Full crystallographic data, excluding structure factors, are provided in Electronic Supplementary Information and have been deposited at the Cambridge Crystallographic Data Centre, CCDC nos. 209051 (**4**), 216572 (**5**) and 209052 (**15**).

2,5-Dibromo-4-nitroacetanilide (2)

2,5-Dibromoacetanilide (**1**;[3] 26.4 g, 90.1 mmol) was added in small portions to H_2SO_4 (120 mL) at –5 °C with stirring using an overhead stirrer, to obtain a clear viscous solution. HNO_3 (36 mL, 70%, d = 1.42 g/cm^3, Fisher) was then added at a speed such that the temperature was controlled between –3 to –5 °C, using a syringe pump through a thin Teflon tubing (*NOTE*: *An external temperature of –10 to –15 °C achieved with an actone/dry-ice cooling bath was needed to maintain the internal temperature under control*). This temperature and stirring were maintained for 1 h after the addition. The clear yellow solution was then poured on to crushed ice and was followed by a suction filtration. The off-white solid, which collected on the filter was washed with a large volume of H_2O to remove the acids. Recrystallisation of the solid from AcOH yielded 26.2 g (86%) of compound **2** as pale-yellow needles; mp 183.9–185.3 °C.

^1H NMR (DMSO-d_6): δ = 2.17 (s, 3 H), 8.32 (s, 1 H), 8.41 (s, 1 H), 9.76 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 23.7, 112.8, 114.2, 129.1, 129.8, 141.0, 145.0, 169.4.

MS (EI): *m*/*z* (%) = 337 (M^+, 12), 295 (100).

Table 1 Crystal Data for Compounds **4** and **15**

Parameters	**4**	**15**
Formula	$C_{14}H_9BrN_2O_2$	$C_{30}H_{22}N_2O_3S$
Formula weight	317.14	490.56
T, K	120	120
Symmetry	Monoclinic	triclinic
Space group	$P2_1/c$ (# 14)	$P\bar{1}$ (# 2)
a, Å	3.9187(3)	9.176(2)
b, Å	22.827(3)	10.247(2)
c, Å	14.152(2)	13.020(2)
α, °	90	84.81(1)
β, °	90.34(2)	86.91(1)
γ, °	90	79.00(1)
V, Å^3	1265.9(2)	1196.0(4)
Z	4	2
μ, mm^{-1}	3.25	0.17
Crystal size	0.45 × 0.20 × 0.04	0.60 × 0.27 × 0.10
Transmission	0.3865–0.8812	0.9038–0.9844
Reflections collected	17585	22254
Unique reflections	3706	6970
R_{int}	0.045[a]	0.041
Reflections	2866	5282
$R[F^2 > 2\sigma(F^2)]$	0.027	0.054
w$R(F^2)$, all data	0.066	0.161

[a] 0.114 before absorption correction.

Anal. Calcd for $C_8H_6Br_2N_2O_3$ (337.95): C, 28.43; H, 1.79; N, 8.29. Found: C, 28.40; H, 1.75; N, 8.22.

2,5-Dibromo-4-nitroaniline (3)

2,5-Dibromo-4-nitroacetanilide (**2**; 7.0 g, 20.7 mmol) was added with stirring to 70% w/w H_2SO_4[15] (140 mL) in portions. The mixture was then gradually heated until the solid was dissolved to yield a clear yellow solution, which was stirred with heating for 1 h, then cooled until yellow crystals appeared. H_2O (200 mL) was added slowly into the flask with stirring. The mixture was then stored at r.t. for 1 h. Bright-yellow crystals of **3** (5.7 g, 93%) were obtained by suction-filtration of the mixture, and recrystallisation from MeOH; mp 182.9–183.9 °C.

^1H NMR (200 MHz, DMSO-d_6): δ = 6.86 (s, 2 H), 7.09 (s, 1 H), 8.21 (s, 1 H).

^{13}C NMR (200 MHz, DMSO-d_6): δ = 104.1, 115.5, 118.1, 131.4, 136.0, 151.5.

MS (EI): *m*/*z* (%) = 296 (M^+, 84), 266 (100).

Anal. Calcd for $C_6H_4Br_2N_2O_2$ (295.92): C, 24.35; H, 1.36; N, 9.47. Found: C, 24.34; H, 1.34; N, 9.41.

2-Bromo-4-nitro-5-phenylethynylaniline (4)

A mixture of 2,5-dibromo-4-nitroaniline (**3**; 2.96 g, 10 mmol), phenylacetylene (1.1g, 10.8 mmol), $Pd(PPh_3)_2Cl_2$ (150 mg) and CuI (75 mg) in freshly distilled THF (10 mL) was heated at 50 °C until the organic solids were dissolved. Et_3N (20 mL) was added and the resulting clear yellow solution was stirred at r.t. for 15 min, at 50 °C for 12 h, then at 90 °C for 1 h to yield a brown suspension. The mixture was cooled to r.t. and Et_2O (50 mL) was added, followed by suction-filtration to remove the solid. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column eluting with CH_2Cl_2–petroleum ether (3:1) to afford a yellow solid, which was recrystallised first from MeOH–H_2O, then from $CHCl_3$–hexane to give compound **4** as yellow needles (2.99 g, 94%); mp 124.7–125.4 °C. A single crystal for X-ray analysis was prepared by slow evaporation of a $CHCl_3$ solution of the compound.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (s, 2 H), 6.94 (s, 1 H), 7.37 (m, 3 H), 7.58 (m, 2 H), 8.35 (s, 1 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 85.3, 96.8, 106.8, 118.3, 120.1, 122.4, 128.4, 129.2, 130.4, 132.0, 139.4, 148.5.

MS (EI): *m*/*z* = 318 (M^+, 100%).

Anal. Calcd for $C_{14}H_9BrN_2O_2$ (317.14): C, 53.02; H, 2.86; N, 8.83. Found: C, 52.78; H, 2.81; N, 8.85.

2-(3-Hydroxy-3-methylbutynyl)-4-nitro-5-phenylethynylaniline (5)

2-Bromo-4-nitro-5-phenylethynylaniline (**4**; 1.755 g, 5.53 mmol) and 2-methyl-3-butyn-2-ol (1.86 g, 22 mmol) were dissolved in freshly distilled Et_3N (40 mL). $Pd(PPh_3)_2Cl_2$ (123 mg) and CuI (61 mg) were added to the solution and the mixture was stirred and heated at 90 °C for 3 h. The mixture was cooled to r.t. and then brought to dryness by vacuum evaporation. Column chromatography of the dark-yellow oily residue (silica gel, CH_2Cl_2 with 20% EtOAc) yielded compound **5** as a yellow amorphous solid (1.63 g, 92%), which gave yellow crystals by adding cyclohexane into its CH_2Cl_2 solution; mp 145.0–145.9 °C. A single crystal was obtained by slow evaporation of its $CDCl_3$ solution.

^{1}H NMR ($CDCl_3$): δ = 1.64 (s, 6 H), 4.84 (s, 2 H), 6.87 (s, 1 H), 7.37 (m, 3 H), 7.58 (m, 2 H), 8.16 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 31.4, 65.7, 76.2, 85.9, 97.2, 102.0, 106.5, 117.8, 120.8, 122.4, 128.4, 129.2, 130.2, 132.0, 138.9, 151.3.

MS (EI): *m*/*z* (%) = 320 (M^+, 40), 105 (100).

Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.34): C, 71.24; H, 5.03; N, 8.74. Found: C, 69.92; H, 4.96; N, 8.58.

2-Ethynyl-4-nitro-5-phenylethynylaniline (6)

Compound **5** (1.62 g, 5.06 mmol) was dissolved in anhyd benzene (50 mL, Aldrich) by heating and stirring under argon. NaH (110 mg, 60% dispersion in mineral oil, Aldrich) was added in one portion and the mixture was refluxed for 5–7 h (TLC monitoring). The reaction mixture was cooled to r.t. and Celite (ca. 1 g) was added followed by filtration through a Celite pad under vacuum. The filtrate was evaporated in vacuo and the residue was column chromatographed (silica gel, CH_2Cl_2) to afford a bright yellow solid, which recystallised from $CHCl_3$–hexane as yellow needles (1.31 g, 98%); mp 104.2–104.8 °C.

^{1}H NMR ($CDCl_3$): δ = 3.52 (s, 1 H), 5.04 (s, 2 H), 6.87 (s, 1 H), 7.36 (m, 3 H), 7.57–7.60 (m, 2 H), 8.21 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 77.7, 85.2, 85.8, 97.3, 105.5, 117.9, 121.1, 122.2, 128.3, 129.1, 130.5, 131.9, 138.5, 151.9.

MS (EI): *m*/*z* = 262 (M^+, 100 %).

Anal. Calcd for $C_{16}H_{10}N_2O_2$ (262.26): C, 73.27; H, 3.84; N, 10.68. Found: C, 73.00; H, 3.85; N, 10.56.

***O*-4-Iodophenyl *N*,*N*-Dimethylthiocarbamate (7)**

This is a modification of the reported general method.[9] 4-Iodophenol (22.0 g, 0.1 mol) was dissolved in anhyd DMF (100 mL, Aldrich). NaH (60% dispersion, 4.0 g, 0.1 mol) was added in small portions with stirring. The mixture was stirred at r.t. for 10 min, then gradually heated to 80 °C and stirred for 30 min until the H_2 gas evolution had ceased. The heating bath was removed and the solution was allowed to cool to r.t., followed by the addition of *N*,*N*-dimethylthiocarbamoyl chloride (15.0 g, 0.12 mol) portionwise with stirring. The mixture was then stirred at r.t. for 12 h and Et_2O (200 mL) was added to the mixture. The solid, which formed during the reaction was removed by suction-filtration. The filtrate was then evaporated and the residue was column chromatographed on silica gel (eluent: CH_2Cl_2) to afford a pale-yellow solid. Recrystallisation of the solid from $CHCl_3$–hexane yielded **7** as large white crystals (27.5 g, 90%); mp 111.0–112.2 °C (Lit.[9] mp 109.5–110.5 °C).

^{1}H NMR ($CDCl_3$): δ = 3.33 (s, 3 H), 3.44 (s, 3 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.69 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 38.8, 43.3, 90.2, 125.0, 138.2, 153.8.

MS (EI): *m*/*z* (%) = 307 (M^+, 24), 72 (100).

Anal. Calcd for $C_9H_{10}INOS$ (307.15): C, 35.19; H, 3.28; N, 4.56. Found: C, 35.58; H, 3.48; N, 4.50.

***S*-4-Iodophenyl *N*,*N*-Dimethylthiocarbamate (8)**

The flask containing **7** (8.71 g, 28.4 mmol) was placed in a Kugelrohr apparatus and heated to 235 °C with spinning. The melt gradually darkened from colourless to light brown. TLC (silica gel, CH_2Cl_2) or ^{1}H NMR analysis was needed to determine the end point of the reaction after ca. 1 h heating. The reaction should be stopped at about 90% conversion based on the NMR integrals. (*Note*: Attention should be paid to the final stage of the reaction as excess heating can result in significant decomposition). The crude product was purified by column chromatography (silica gel, CH_2Cl_2), then recrystallised from cyclohexane affording **8** as off-white plates (7.18 g, 82%); mp 89.5–90.6 °C (Lit.[16] mp 87.5–88.8 °C).

^{1}H NMR ($CDCl_3$): δ = 3.02 (s, 3 H), 3.06 (s, 3 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 36.9, 95.7, 128.7, 137.2, 138.0, 166.1.

MS (EI): *m*/*z* (%) = 307 (M^+, 100).

Anal. Calcd for $C_9H_{10}INOS$ (307.15): C, 35.19; H, 3.28; N, 4.56. Found: C, 35.23; H, 3.29; N, 4.51.

4-Iodothiophenol (9)

To the degassed solution of compound **8** (7.6 g, 24.7 mmol) in MeOH (150 mL) was added KOH pellets (4.0 g). The mixture was heated to reflux and stirred for 1 h under argon. The solution was cooled to r.t. and HCl acid was added until the pH was ca. 1, followed by the slow addition of H_2O (ca. 100 mL) with stirring. A pale-yellow crystalline solid was collected by suction-filtration, then washed with a large volume of H_2O to yield 4-iodothiophenol (**9**) as white crystals (5.68 g, 97%); mp 84.7–85.3 °C (Lit.[17] mp 86 °C). The solid was essentially analytically pure and was used for the subsequent reactions without further purification.

^{1}H NMR ($CDCl_3$): δ = 3.43 (s, 1 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 90.1, 130.9, 131.1, 138.0.

MS (EI): *m*/*z* = 236 (M^+, 100%).

Anal. Calcd for C_6H_6IS (236.07): C, 30.53; H, 2.13. Found; C, 30.66; H, 2.55.

1-Acetylthio-4-iodobenzene (10)

4-Iodothiophenol (**9**; 2.13 g, 9.02 mmol) was dissolved in pyridine (30 mL, dried over NaOH pellets and degassed). Acetyl chloride

(1.5 mL, 21 mmol) was syringed in slowly with vigorous stirring under argon. The mixture was stirred for an additional 15 min followed by the addition of H_2O and crushed ice. The precipitated pale-yellow solid was collected by suction-filtration then washed with H_2O. Column chromatography of the crude product on silica gel (CH_2Cl_2–petroleum ether, 1:1) yielded compound **10** as a white solid (2.47 g, 98%). The solid was recrystallised from MeOH–H_2O to form white crystals; mp 57.0–57.7 °C (Lit.[18] mp 56–57 °C).

^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 30.2, 95.9, 127.7, 135.9, 138.3, 193.1.

MS (EI): *m*/*z* (%) = 278 (M^+, 24), 236 (100).

Anal. Calcd for C_8H_7IOS (278.11): C, 34.55; H, 2.54. Found: C, 34.55; H, 2.53.

2-(4-Acetylthiophenylethynyl)-4-nitro-5-phenyethynylaniline (11)

A flame-dried flask was charged with compound **6** (144.6 mg, 0.55 mmol), compound **10** (0.23 g, 0.83 mmol), $Pd(PPh_3)_2Cl_2$ (23 mg), CuI (14 mg), freshly distilled THF (30 mL) and Et_3N (5 mL). The mixture was stirred at r.t. for 3.5 h to obtain an orange solution. The reaction was then continued, by heating at 50 °C for 1.5 h. The mixture was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 and column chromatographed (silica gel, CH_2Cl_2). A further purification by recrystallisation of the yellow solid from benzene afforded compound **11** as bright-yellow crystals (128 mg, 56%); mp 175.8–176.6 °C.

^{1}H NMR ($CDCl_3$): δ = 2.45 (s, 3 H), 4.90 (s, 2 H), 6.92 (s, 1 H), 7.39 (m, 3 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.59 (m, 2 H), 8.28 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 30.3, 84.8, 85.9, 96.4, 97.6, 106.8, 118.0, 121.0, 122.5, 123.2, 128.4, 129.1, 129.2, 130.2, 132.06, 132.11, 134.4, 139.4, 151.1, 193.3.

MS (EI): *m*/*z* (%) = 412 (M^+, 47), 43 (100).

Anal. Calcd for $C_{24}H_{16}N_2O_3S$ (412.46): C, 69.89; H, 3.91; N, 6.79. Found: C, 69.98; H, 3.86; N, 6.83.

4-Bromophenyl 4-Methoxybenzyl Sulfide (12)

To a degassed solution of 4-bromothiophenol (3.78 g, 20 mmol) in anhyd DMF (30 mL) was added solid K_2CO_3 (2.76 g, 20 mmol). The mixture was stirred under argon for 10 min followed by the dropwise addition of 4-methoxybenzyl chloride (3.13 g, 20 mmol). The mixture was then stirred at r.t. for 12 h and at 100 °C for an additional 1 h to afford a white suspension. A white solid precipitated gradually on slow addition of H_2O (50 mL). The solid was collected by suction-filtration, then purified by recrystallisation from MeOH to yield compound **12** as white crystals (5.49 g, 89%); mp 100.5–101.0 °C.

^{1}H NMR ($CDCl_3$): δ = 3.79 (s, 3 H), 4.05 (s, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 38.5, 55.2, 113.9, 120.2, 128.9, 129.9, 131.4, 131.8, 135.6, 158.8.

MS (EI): *m*/*z* (%) = 310 (M^+, 10), 121 (100).

Anal. Calcd for $C_{14}H_{13}BrOS$ (309.22): C, 54.38; H, 4.24. Found: C, 54.50; H, 4.22.

4-(3-Hydroxy-3-methylbutynyl)phenyl 4-Methoxylbenzyl Sulfide (13)

A mixture of **12** (1.55 g, 5 mmol), 2-methyl-3-butyn-2-ol (1.68 g, 20 mmol), $Pd(PPh_3)_2Cl_2$ (74 mg), CuI (37 mg) and Et_3N (30 mL) was refluxed for 2 h. Additional $Pd(PPh_3)_2Cl_2$ (80 mg) and CuI (40 mg) were added and the reflux was continued for a further 10 h. The resulting hot brown suspension was suction-filtered through a Celite pad and the filter cake was washed with Et_2O. The filtrate was evaporated and the residue was column chromatographed (silica gel, 10% Et_2O in CH_2Cl_2). White crystals of **13** were obtained (1.44 g, 92%) after recrystallisation from MeOH; mp 120.4–121.4 °C.

^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 6 H), 2.11 (s, 1 H), 3.80 (s, 3 H), 4.10 (s, 2 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.216 (d, *J* = 8.7 Hz, 2 H), 7.224 (d, *J* = 8.7 Hz, 2 H), 7.31 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 31.4, 37.8, 55.2, 65.6, 81.7, 94.1, 113.9, 120.1, 128.71, 128.75, 129.9, 131.9, 137.3, 158.8.

MS (EI): *m*/*z* (%) = 294 (M^+ – 18, 19), 121 (100).

Anal. Calcd for $C_{19}H_{20}O_2S$ (312.43): C, 73.04; H, 6.45. Found: C, 72.82; H, 6.45.

4-(4-Methoxybenzylthio)phenylacetylene (14)

To a solution of **13** (1.88 g, 6 mmol) in anhyd benzene (40 mL) was added NaH (60% dispersion, 0.12 g, 3 mmol) and the mixture was refluxed for 1 h under argon. Benzene was removed under vacuum and the residue was column chromatographed (silica gel, CH_2Cl_2). Recrystallisation of the product from MeOH yielded **14** as white crystals (1.2 g, 78%); mp 125.8–126.3 °C.

^{1}H NMR ($CDCl_3$): δ = 3.07 (s, 1 H), 3.78 (s, 3 H), 4.09 (s, 2 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 4 H), 7.36 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 37.7, 55.2, 77.5, 83.3, 113.9, 119.4, 128.5, 128.6, 129.9, 132.3, 138.2, 158.8.

MS (EI) *m*/*z* (%) = 254 (M^+, 65), 121 (100).

Anal. Calcd for $C_{16}H_{14}OS$ (254.35): C, 75.55; H, 5.55. Found: C, 75.48; H, 5.54.

2-[4-(4-Methoxybenzylthio)phenylethynyl]-4-nitro-5-phenylethynylaniline (15)

The solution of **4** (0.317 g, 1 mmol), **14** (0.254 g, 1 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg), CuI (9.6 mg) in Et_3N (15 mL) was refluxed for 2 h. TLC analysis of the reaction mixture indicated that **14** was completely consumed. The mixture was cooled to r.t. and then suction-filtered. The solid on the filter was washed with Et_2O and then column chromatographed twice on silica gel. The first column was eluted with 20% petroleum ether in CH_2Cl_2 and the second column was eluted with $CHCl_3$ to afford **15** as a yellow solid (0.11 g, 22%). A crystal for X-ray analysis was obtained by recrystallisation from chlorobenzene; mp 200.7–201.5 °C.

^{1}H NMR ($CDCl_3$): δ = 3.81 (s, 3 H), 4.15 (s, 2 H), 4.84 (s, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 6.94 (s, 1 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.7 Hz, 2 H), 7.40 (m, 5 H), 7.62 (m, 2 H), 8.27 (s, 1 H).

MS (EI): *m*/*z* (%) = 490 (M^+, 7), 121 (100).

Anal. Calcd for $C_{30}H_{22}N_2O_3S$ (490.57): C, 73.45; H, 4.52; N, 5.71. Found: C, 73.24; H, 4.47; N, 5.62.

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