

Synthetic routes to 3-alkylsulfanyl-6-aryl-diketopyrrolo[3,4-*c*]pyrroles—a class of efficient, visible light excitable fluorophores

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Sulfide derivatives of diketopyrrolo[3,4-*c*]pyrrole (SDPPs) were prepared in a one-pot procedure from arylpyrrolinones, isothiocyanates and alkylating agents, and their properties as fluorophores were evaluated.

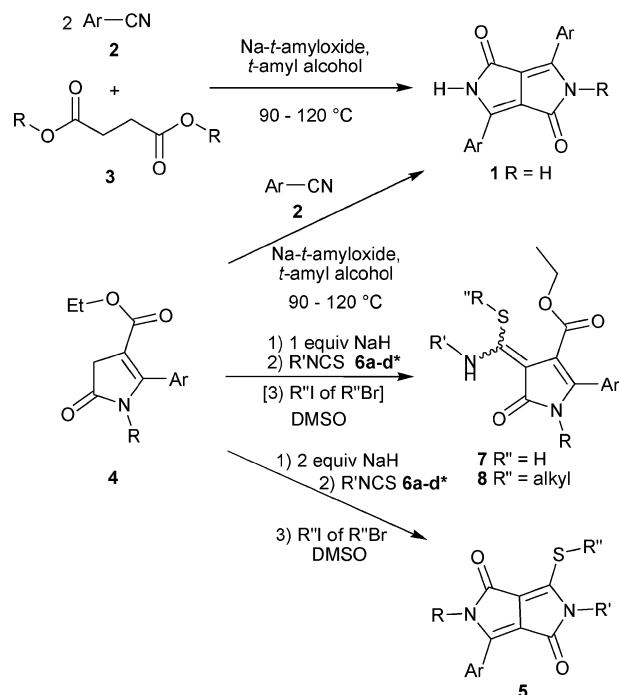
Introduction

In our research group we are interested in fluorophores that combine high fluorescence quantum yields with absorption and emission in the visible wavelength region.^{1–3} Such fluorophores have the advantage to be useful in measurements using glass optics and low energetic radiation. Moreover, they can be incorporated in biosensors because they absorb and emit light outside the wavelength region of autofluorescence of biological cell components.

Diketopyrrolo[3,4-*c*]pyrrole (DPP) **1** is a well known pigment with a high colour strength and photostability.⁴ DPP is also a fluorophore with fluorescence in the visible region and a high fluorescence quantum yield.⁵ Besides the use of DPP in the pigment industry, there is an increasing use of DPP for more advanced (electronic) applications. Since the end of the 1980s, many applications for DPP derivatives have been proposed, such as their use as charge-generating materials for laser printers, erasable optical information carriers or as electroluminescent elements.^{6–9} DPP has recently been derivatized for the incorporation of different materials like conjugated polymers, liquid crystals and metal complexes in view of processing DPP derivatives in OLEDs, LCD applications, data carriers and NLO applications.^{10–15} In the patent literature, the application of electroluminescent materials like π -conjugated polymers with DPP in the backbone or some specific heteroaromatic DPP derivatives with a very efficient use of electrical energy and strong luminescence, can be found.¹⁶

Recently, we synthesized DPP derivatives which could be incorporated into supramolecular systems. For instance, dendrimers were synthesized with DPP as a core.^{3,5} Furthermore, DPP was used as a building block for rigid oligomers of well defined length.² Several conjugates were prepared of a Ca^{2+} -selective podand¹⁷ and DPP,¹⁸ which could be useful as intracellular fluorescent Ca^{2+} indicators.

DPP can be synthesized by condensation of 2 equivalents of an aromatic nitrile **2** with 1 equivalent of a dialkyl succinate **3** under harsh conditions involving the use of a strong base and high reaction temperatures (Scheme 1). This is the most general method used in industrial pigment production.⁴ However, only robust substituents are tolerated such as halogens, aromatic, aliphatic and alkoxy groups. Neither nitro groups nor electrophilic groups are compatible with these conditions.



Scheme 1 DPP synthesis under harsh conditions and one-pot synthesis of SDPP **5**, thioaminals **7** or *S*-alkylated thioaminals **8**. * **6a** $\text{R}' = \text{Me}$; **6b** $\text{R}' = \text{Ph}$; **6c** $\text{R}' = 4\text{-Me}_2\text{NC}_6\text{H}_4$; **6d** $\text{R}' = 4\text{-NO}_2\text{C}_6\text{H}_4$.

Recently, Morton *et al.* published the condensation of pyrrolinones **4**¹⁹ with nitriles **2**, affording asymmetric DPP derivatives under similar conditions.^{20,21} In a subsequent paper,²² imidoyl chlorides were also used in combination with pyrrolinones, affording triaryl DPPs.

Results and discussion

We are interested in extending the variety of substituents accessible, as well as breaking the symmetry of the DPP chromophore. This can be achieved by using less drastic reaction conditions or by synthesising asymmetric derivatives which can react selectively at one position. For example, it is interesting to have only one free amide NH group on the DPP, which could be used for selective reactions.

A new synthetic strategy to functionalize asymmetric diaryl-DPP analogues was devised based on mild cross-coupling

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reactions. In this way a large variety of groups or functions could be attached to the chromophore, *e.g.*, by the Liebeskind–Srogl reaction.²³ This reaction of arylboronic acids with thioesters, thioalkynes and several thioethers affords arylated derivatives under very mild (*i.e.*, neutral) conditions. The synthesis of a reactive thioether derivative of DPP **5** seemed possible starting from pyrrolinones **4** and isothiocyanates **6**.

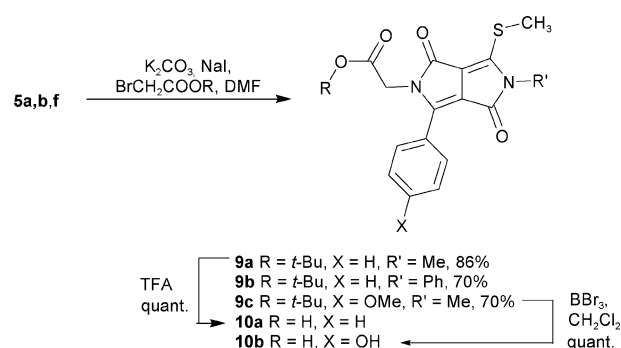
The C-3 position of pyrrolinones **4a,b** can easily be deprotonated, and in fact sodium hydride gives complete deprotonation. Addition of isothiocyanates **6a–d** to these deprotonated pyrrolinones **4a,b** gave intermediate thioaminals **7** (Scheme 1, Table 1). By subsequent addition of an equimolar quantity of base, isothiocyanate and an alkylating agent to pyrrolinone **4a,b**, this sequence yielded the selectively *S*-alkylated **8**. When the amount of base was doubled, the desired ring-closed alkylsulfanylpyrrolopyrroles (SDPPs) **5a–f** were obtained (Scheme 1, Table 1). The yields of **5** were fair (54–66%) except for compound **5d** (derived from **4a** and 4-dimethylaminophenyl isothiocyanate **6c**). In this case the expected SDPP **5d** was obtained in only 37% yield, and this was at least in part the result of overalkylation, leading to the *N,N*-dimethyl SDPP **5e** (9% yield).

Compound **5e** could be prepared more effectively from **4d** in 60% yield using an analogous procedure. We failed to obtain cyclized products of type **5** when starting from 4-nitrophenyl isothiocyanate **6d**, probably due to the low nucleophilicity of the nitrogen atom in this case. All reaction steps leading to compounds **5** could be performed at room temperature.

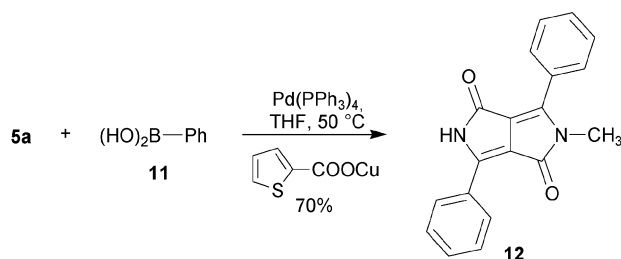
Also, *N*-substituted pyrrolinone **4c** could be used for the preparation of *N,N*-dialkylated SDPP **5g**, albeit in somewhat lower yield (31%).

Most SDPPs **5** are only sparingly soluble in common organic solvents such as dichloromethane, ethyl acetate or alcohols. Replacement of the methyl group in **5b** by the larger benzyl substituent in **5c** was found to increase the solubility. *N*-Alkylation of the SDPPs **5a, b** and **f** with a *tert*-butyl-protected acetate group on the free amide function, providing **9a, b** and **c**, respectively, increased the solubility because in the latter compounds hydrogen bond formation is impossible (Scheme 2). In order to prepare water-soluble DPP derivatives, the easy deprotection of the acetate group of **9a** with trifluoroacetic acid (TFA) gave SDPP **10a** in quantitative yield. This compound was found to be soluble in slightly basic aqueous media. From the SDPP derivative **9c** the acetate group and the phenol function could be deprotected quantitatively using BBr₃ affording the product **10b**.

Under Liebeskind–Srogl conditions,²³ SDPP **5a** could be coupled with phenylboronic acid **11** to provide DPPD **12** in good yield (Scheme 3). Unfortunately, the reaction was not complete



Scheme 2 *N*-Alkylation of SDPPs **5a, b** and **f**.



Scheme 3 Transformation of SDPP **5** to monoalkylated DPP **12**.

even after prolonged reaction time, which necessitated additional purification by column chromatography. Electron-rich or electron-poor arylboronic acids gave low yields or no reaction product.

Previously, the mono-*N*-alkyl-DPP **12** was difficult to prepare because of the number of additional steps and purifications required to prepare **12** starting from DPP **1**. Indeed, Boc protection of both amide functions and selective removal of one Boc group was necessary. Direct monoalkylation of DPP is difficult because the monoalkylated product is more soluble than the starting material and hence more reactive towards further *N*-alkylation.²⁴

To study the spectroscopic properties of the new SDPP compounds, some representative UV/vis absorption and fluorescence spectra were recorded in different solvents. As an example, Fig. 1 shows the absorption and steady-state fluorescence emission spectra of **5b** and **5g** in toluene, and **9b** in methanol. Typically, the

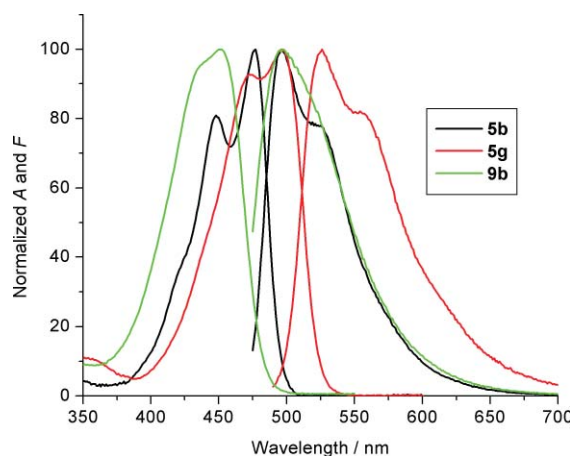


Fig. 1 Normalized absorption (*A*) and fluorescence emission (*F*) spectra (excitation at 470 nm) of **5b** (black) and **5g** (red) in toluene and **9b** (green) in methanol.

Table 1 One-pot synthesis of SDPP **5**

| SDPP | Ar | R | R' | R'' | Yield (%) ^a |
|-----------|------------------------------------|-----------------|--|-----------------|------------------------|
| 5a | Ph | H | CH ₃ | CH ₃ | 58 |
| 5b | Ph | H | Ph | CH ₃ | 66 |
| 5c | Ph | H | Ph | Bn | 54 |
| 5d | Ph | H | 4-Me ₂ NC ₆ H ₄ | CH ₃ | 37 |
| 5e | Ph | CH ₃ | 4-Me ₂ NC ₆ H ₄ | CH ₃ | 60 |
| 5f | 4-MeOC ₆ H ₄ | H | CH ₃ | CH ₃ | 62 |
| 5g | 2-Thienyl | Allyl | CH ₃ | CH ₃ | 31 |

^a Isolated yield.

compounds have absorption spectra with an intense absorption band ranging from 452 nm for **9b** in methanol, to 497 nm for **5g** in toluene. An additional (more or less pronounced) shoulder is observed on the short-wavelength side. The emission spectra show a Stokes-shifted fluorescence emission band of mirror image shape. The fluorescence quantum yields are for most compounds higher than 0.8 and often reach 1.0. The excitation maxima coincide exactly with the absorption maxima.

Compound **5b** was studied in some more detail. The absorption spectra of **5b** are only slightly affected by solvent polarity: the maximum being slightly shifted hypsochromically (*ca.* 7 nm) when the solvent is changed from toluene (477 nm) to acetonitrile and methanol (470 nm). They all show two absorption maxima: (1) a strong S_0-S_1 transition with a maximum between 470 and 477 nm, (2) the second maximum, or shoulder, at the high-energy side, is centered at about 445 nm, which is attributed to the 0–1 vibrational transition. The molar absorption coefficients ϵ_{max} at the maximum for the new SDPP analogues are relatively high. For example, for compound **5b**, ϵ_{max} equals $(19 \pm 2) \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$ in ethyl acetate and $(20.7 \pm 0.8) \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$ in chloroform.

The rather low fluorescence quantum yield ϕ_f for **5d** in methanol and toluene may be rationalized by an efficient quenching *via* an intramolecular charge transfer process in the excited state from the tertiary amino group to the DPP moiety. Protonation drastically alters the electron-donating properties of the tertiary amino group and consequently “switches off” any charge-transfer process, resulting in a large fluorescence enhancement (ϕ_f rises from 0.001 to 0.69). Simultaneously, the full width at half maximum (fwhm_{abs}) of the absorption band slightly decreases upon addition of HClO_4 (from 3513 cm^{-1} for **5d** in methanol, to 3322 cm^{-1} for **5d-H**⁺ in acidified methanol). Table 2 summarizes the photophysical data of several new SDPP derivatives.

Conclusion

The novel alkylthiopyrrolopyrroles (SDPP) **5** are valuable fluorophores with high fluorescence quantum yields (often approach-

ing 1.0) that are excitable with visible light (above 450 nm). They possess several synthetic advantages compared to diaryl-DPP **1**. SDPPs can easily be prepared starting from pyrrolinones **4**, isothiocyanates **6** and alkylating agents in a one-pot three-component reaction at room temperature. A moderate number of functional groups can be introduced *via* the substituents on the aryl group of **4** or *via* the *N*-substituents of **4** or **6**. Through *N*-alkylation of the remaining unsubstituted nitrogen atom, a variety of functional groups can be incorporated. Using the very mild Liebeskind–Srogl conditions it is possible to convert the SDPP into the corresponding monoalkylated diaryl-DPP.

Experimental

Spectroscopic measurements

The absorption measurements were performed on a Perkin-Elmer Lambda 40 UV/Vis spectrophotometer. Corrected steady-state excitation and emission spectra were recorded on a SPEX Fluorolog. For the determination of the relative fluorescence quantum yields (ϕ_f), only dilute solutions with an absorbance below 0.1 at the excitation wavelength (470 nm for all measured compounds) were used. Rhodamine 6G in water ($\phi_f = 0.76$) was used as a fluorescence standard.²⁵ The ϕ_f values reported in this work are the averages of multiple (generally 3), fully independent measurements. All measurements were done at 20 °C using non-degassed samples. The absorption spectra match the excitation spectra in all cases.

General procedure for the compounds **5**

6-Phenyl-2-methyl-3-(methylsulfanyl)-1,4-(2*H*,5*H*)-dioxopyrrolo[3,4-*c*]pyrrole (5a**).** To a solution of pyrrolinone **4a** (Ar = Ph, R = H, 924 mg, 4.00 mmol), in DMSO (10 mL) under argon atmosphere was added NaH (264 mg, 8.00 mmol, 80% in oil), and after 15 min methyl isothiocyanate (297 mg, 4.40 mmol). The mixture was stirred at room temperature for 6 h. After cooling the mixture to 0 °C, methyl iodide (624 mg, 4.40 mmol) was added

Table 2 Absorption and fluorescence data for some of the SDPP compounds in different solvents

| Compound | Solvent | $\lambda_{\text{abs}}/\text{nm}^a$ | $\lambda_{\text{em}}/\text{nm}^b$ | $\Delta\bar{\nu}/\text{cm}^{-1}^c$ | $\text{fwhm}_{\text{abs}}/\text{cm}^{-1}^d$ | ϕ_f^e |
|-----------|------------------------|------------------------------------|-----------------------------------|------------------------------------|---|------------|
| 5b | MeOH | 470 | 499 | 1237 | 2672 | 0.84 |
| | CH_3CN | 470 | 493 | 993 | 3092 | 0.94 |
| | Ethyl acetate | 474 | 492 | 772 | 2868 | 0.87 |
| | THF | 475 | 494 | 810 | 2898 | 0.87 |
| | CHCl_3 | 474 | 494 | 854 | 2680 | 1.00 |
| | Toluene | 477 | 497 | 844 | 2561 | 1.00 |
| 5d | MeOH | 459 | 513 | 2293 | 3513 | 0.001 |
| | MeOH + HClO_4 | 458 | 501 | 1874 | 3322 | 0.69 |
| | Toluene | 469 | 505 | 1520 | 3630 | 0.002 |
| 5g | MeOH | 487 | 539 | 1981 | 3439 | 0.40 |
| | Toluene | 497 | 526 | 1109 | 2979 | 0.71 |
| 5f | MeOH | 476 | 506 | 1246 | 2508 | 0.78 |
| | Toluene | 482 | 497 | 626 | 2675 | 0.91 |
| 9a | MeOH | 455 | 498 | 1898 | 3323 | 0.87 |
| | Toluene | 464 | 500 | 1552 | 3147 | 1.00 |
| 9b | MeOH | 452 | 497 | 2003 | 3233 | 0.88 |
| | Toluene | 459 | 499 | 1746 | 3118 | 1.00 |

^a The position of the absorption maximum. The absorption spectra match the excitation spectra in all cases. ^b The position of the fluorescence emission maximum. All samples were excited at 470 nm. ^c Stokes shift (in cm^{-1}). ^d Full width at half maximum of the absorption band (in cm^{-1}). ^e Fluorescence quantum yield (all samples were excited at 470 nm).

and the mixture was stirred for 12 h at room temperature. The mixture was then added to an ice/water mixture (150 mL) and 1 mL of acetic acid, and stirred for 15 min. The finely divided precipitate was filtered and washed with water and cold methanol until colorless, furnishing pure **5a** (640 mg, 58%) as a bright orange powder. δ_{H} (300 MHz, CDCl_3 - CF_3COOD): 3.17 (s, 3H), 3.24 (s, 3H), 7.48–7.51 (m, 3H), 8.21–8.23 (m, 2H), 8.97 (s, 1H); δ_{C} (75 MHz, CDCl_3 - CF_3COOD): 16.5, 28.6, 108.2, 113.0, 116.8, 127.0, 127.7, 129.8, 132.7, 141.3, 160.4, 162.4; LR-MS (CI): 273 MH^+ ; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 476 nm (4.292), 450 nm (4.213); mp 284 °C.

2,6-Diphenyl-3-(methylsulfanyl)-1,4-(2H,5H)-dioxopyrrolo[3,4-c]pyrrole (5b). Prepared in the same way from phenyl isothiocyanate and **4a** in 66% yield. δ_{H} (300 MHz, CDCl_3) 3.09 (s, 3H), 7.31–7.36 (m, 3H), 7.46–7.53 (m, 5H), 8.19–8.23 (m, 2H), 8.48 (s, 1H); δ_{C} (75 MHz, CDCl_3) 16.6, 109.4, 111.5, 128.5, 128.6, 129.6, 130.0, 130.2, 132.6, 135.2, 143.7, 151.8, 160.5, 162.8; LR-MS (CI): 335 MH^+ ; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 472 nm (4.485), 444 nm (4.327); mp 283–285 °C.

2,6-Diphenyl-3-(benzylsulfanyl)-1,4-(2H,5H)-dioxopyrrolo[3,4-c]pyrrole (5c). Prepared in the same way, using benzyl bromide instead of methyl iodide, from phenyl isothiocyanate and **4a** in 54% yield. δ_{H} (300 MHz, CDCl_3) 5.00 (s, 2H), 7.25–7.31 (m, 7H), 7.44–7.56 (m, 6H), 8.43 (m, 2H), 11.32 (s, 1H); δ_{C} (75 MHz, CDCl_3) 65.7, 86.0, 125.7, 127.7, 127.8, 128.1, 128.2, 128.3, 129.4, 129.5, 129.8, 130.3, 135.1, 135.7, 144.1, 169.9, 173.8, 208.7; LR-MS (CI): 411 MH^+ ; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 475 nm (4.347), 448 nm (4.267); mp 264 °C.

2-(4-(N,N-Dimethylamino)phenyl)-6-phenyl-3-(methylsulfanyl)-1,4-(2H,5H)-dioxopyrrolo[3,4-c]pyrrole (5d). Prepared in the same way, from the corresponding isothiocyanate and **4a** in 37% yield. δ_{H} (300 MHz, CDCl_3) 2.52 (s, 6H), 2.93 (s, 3H), 6.82 (d, 2H, J = 8.8 Hz), 7.10 (d, 2H, J = 9.5 Hz), 7.49–7.53 (m, 3H), 8.28–8.32 (m, 2H), 11.16 (s, 1H); δ_{C} (75 MHz, CDCl_3) a sufficiently high concentration could not be reached; MS (EI, 70 eV) m/z 378 (MH^+ , 32), 377 (M^+ , 100), 331 (14), 330 (74), 302 (18), 134 (17); HRMS (EI+): calcd for $\text{C}_{21}\text{H}_{19}\text{O}_2\text{N}_3\text{S}$ (M^+) 377.11980; found 377.12029; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 474 nm (4.45), 449 nm (4.262); mp >300 °C.

2-(4-(N,N-Dimethylamino)phenyl)-5-methyl-6-phenyl-3-(methylsulfanyl)-1,4-(2H,5H)-dioxopyrrolo[3,4-c]pyrrole (5e). Prepared following the general procedure, from the corresponding isothiocyanate and **4d** (Ar = Ph, R = Me), in 60% yield. δ_{H} (300 MHz, CDCl_3) 2.90 (s, 6H), 3.04 (s, 3H), 3.36 (s, 3H), 6.75 (d, 2H, J = 8.9 Hz), 7.13 (d, 2H, J = 9.1 Hz), 7.43–7.49 (m, 3H), 7.79–7.82 (m, 2H), 11.12 (s, 1H); δ_{C} (75 MHz, CDCl_3) 16.4, 30.0, 40.7, 108.5, 109.6, 112.4, 122.7, 128.3, 129.1, 129.3, 131.0, 144.5, 151.0, 156.0, 156.1, 161.3, 162; MS (EI, 70 eV) m/z 391 (M^+ , 100), 345 (19), 344 (95), 172 (11); calcd for $\text{C}_{22}\text{H}_{21}\text{O}_2\text{N}_3\text{S}$ (M^+) 391.13545; found 391.13545; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 464 nm (4.277), 441 nm (4.219); mp 229 °C.

6-(4-Methoxyphenyl)-2-methyl-3-methylsulfanyl-1,4-(2H,5H)-dioxopyrrolo[3,4-c]pyrrole (5f). Prepared following the general procedure, starting from **4b** (Ar = 4-anisyl, R = H), in 62% yield. δ_{H} (300 MHz, CDCl_3) 3.06 (s, 3H), 3.07 (s, 3H), 4.14 (s, 3H), 6.86 (d, 2H, J = 9.2 Hz), 7.57 (d, 2H, J = 9.1 Hz), 9.00 (s, 1H); δ_{C} (75 MHz,

CDCl_3); 15.5, 27.62, 55.04, 107.4, 109.2, 114.6, 120.3, 129.7, 142.5, 149.0, 159.8, 161.5, 162.0; MS (EI, 70 eV) m/z 302 (M^+ , 100), 287 (19), 269 (19), 256 (11), 255 (56). HRMS (EI+): calcd for $\text{C}_{15}\text{H}_{14}\text{O}_3\text{N}_2\text{S}$ (M^+) 302.0725; found 302.0722. UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 480 nm (4.331), 451 nm (4.243); mp 280 °C.

2-Allyl-5-methyl-6-(methylsulfanyl)-3-(2-thienyl)-1,4-(2H,5H)-dioxopyrrolo[3,4-c]pyrrole (5g). Prepared following the general procedure, starting from **4c** (Ar = 2-thienyl, R = allyl), in 31% yield after purification by column chromatography. δ_{H} (300 MHz, CDCl_3) 3.13 (s, 3H), 3.20 (s, 3H), 4.59 (t, 2H, J = 1.8 Hz), 5.11–5.22 (m, 2H), 5.90–6.01 (m, 1H), 7.19 (t, 1H, J = 4.5 Hz), 7.55 (d, 1H, J = 6.4 Hz), 8.54 (m, 2H); δ_{C} (75 MHz, CDCl_3) 16.2, 27.9, 44.1, 107.6, 108.4, 116.7, 128.5, 129.6, 130.5, 133.1, 133.9, 137.9, 152.6, 160.5, 160.7; LR-MS (CI): 319 MH^+ ; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 492 nm (4.321), 308 nm (4.188); mp 143 °C.

General procedure for compounds 9

tert-Butyl-2-(6-(methylsulfanyl)-1,4-dioxo-3,5-diphenyl-4,5-dihydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetate (9b). A suspension of **5b** (100 mg, 0.30 mmol), K_2CO_3 (103 mg, 0.75 mmol) and NaI (100 mg) in DMF (20 mL) was heated for 15 min until **5b** was dissolved. At room temperature *tert*-butyl bromoacetate (98 mg, 73 mL, 0.50 mmol) was added in a drop-wise manner. The reaction mixture was stirred for 12 h at 80 °C. After cooling to room temperature, the mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The organic phase was washed with water (2 × 50 mL) and the aqueous phase was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over MgSO_4 . The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, CH_2Cl_2 –ethyl acetate), furnishing **9b** (46 mg, 34%) as an orange-red powder. δ_{H} (300 MHz, CDCl_3) 1.39 (s, 9H), 3.08 (s, 3H), 4.41 (s, 2H), 7.28–7.31 (m, 2H), 7.42–7.49 (m, 6H), 7.70–7.72 (m, 2H); δ_{C} (75 MHz, CDCl_3) 16.6, 28.3, 44.7, 83.0, 128.1, 128.7, 129.0, 129.3, 129.4, 129.6, 131.2, 134.4, 144.3, 155.1, 160.8, 161.8, 168.1; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 455 nm (4.159), 288 nm (4.006); LR-MS (CI): 449 MH^+ ; mp 127 °C.

tert-Butyl-2-(3-phenyl-5-methyl-6-(methylsulfanyl)-1,4-dioxo-4,5-dihydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetate (9a). Prepared from **5a** according to the general procedure in 86% yield, δ_{H} (300 MHz, CDCl_3) 1.38 (s, 9H), 3.15 (s, 3H), 3.17 (s, 3H), 4.34 (s, 2H), 7.46–7.53 (m, 3H), 7.65–7.70 (m, 2H); δ_{C} (75 MHz, CDCl_3) 16.31, 27.9, 29.4, 44.5, 82.5, 107.3, 110.7, 128.3, 128.7, 129.0, 143.9, 155.1, 161.1, 161.3, 168.1, 169.9; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 456 nm (4.153), 287 nm (4.120); LR-MS (CI): 386 MH^+ ; mp 79 °C.

tert-Butyl-2-(3-(4-methoxyphenyl)-5-methyl-6-(methylsulfanyl)-1,4-dioxo-4,5-dihydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetate (9c). Prepared from **5f** according to the general procedure in 70% yield, δ_{H} (300 MHz, CDCl_3) 1.39 (s, 9H), 3.13 (s, 3H), 3.16 (s, 3H), 3.80 (s, 3H), 4.34 (s, 2H), 6.95 (d, 2H, J = 8.8 Hz), 7.57 (d, 2H, J = 8.8 Hz); δ_{C} (75 MHz, CDCl_3) 16.2, 28.8, 44.6, 55.7, 82.7, 109.8, 114.7, 120.5, 130.6, 144.2, 153.5, 161.1, 161.8, 168.1; UV (CH_2Cl_2): λ_{max} (log ϵ_{max}) = 462 nm (4.308), 298 nm (4.145); LR-MS (CI): 417 MH^+ ; mp 123 °C.

2-(3-Phenyl-5-methyl-6-(methylsulfanyl)-1,4-dioxo-4,5-dihydro-pyrrolo[3,4-c]pyrrol-2(1H)-yl)acetic acid (10a). A solution of **9a** (110 mg, 0.28 mmol) in trifluoroacetic acid (3 mL) was stirred overnight at room temperature. After addition of water, the aqueous layer was extracted with diethyl ether. The collected organic layers were washed with brine and water, and the solvent evaporated under reduced pressure to afford **10a** in 87% yield, δ_{H} (300 MHz, DMSO- d_6): 3.08 (s, 3H), 3.10 (s, 3H), 4.34 (s, 2H), 7.52–7.55 (m, 3H), 7.66–7.70 (m, 2H), 10.27 (s(br), 1H), 13.03 (s(br), 1H); δ_{C} (75 MHz, DMSO- d_6): 18.5, 30.0, 45.8, 108.9, 111.9, 130.2, 131.0, 131.6, 133.5, 145.7, 157.3, 160.8, 161.3, 162.6, 162.8, 172.6; MS (EI, 70 eV) m/z 330 (M^+ , 100), 297 (15), 284 (19), 283 (81); HRMS (EI+): calcd for $C_{16}H_{14}N_2O_4S$ (M^+) 330.06734; found 330.06734; UV (H_2O): λ_{max} = 455 nm; mp 192 °C.

2-(3-(4-Hydroxyphenyl)-5-methyl-6-(methylsulfanyl)-1,4-dioxo-4,5-dihydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetate (10b). Prepared from **9c** in a similar way as for **10a**, in quantitative yield. δ_{H} (300 MHz, DMSO- d_6): 3.07 (s, 3H), 3.09 (s, 3H), 4.37 (s, 2H), 6.90 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.8 Hz), 10.27 (s(br), 1H), 13.03 (s(br), 1H); δ_{C} (75 MHz, DMSO- d_6): 15.7, 27.7, 43.6, 106.6, 108.2, 116.0, 118.3, 130.7, 144.4, 152.2, 160.3, 160.7, 170.4; MS (EI, 70 eV) m/z 346 (M^+ , 100), 313 (25), 302 (15), 300 (12), 299 (63), 255 (14); HRMS (EI+): calcd for $C_{16}H_{14}N_2O_5S$ (M^+) 346.06234; found 346.06257; UV (H_2O , $NaHCO_3$ 3 mM); λ_{max} (log ϵ_{max}) = 466 nm (4.328), 293 (4.064); mp 242 °C.

2-Methyl-3,6-diphenyl-1,4(2H,5H)-dioxopyrrolo[3,4-c]pyrrole (12). A solution of **5a** (136 mg, 0.50 mmol), phenylboronic acid (67 mg, 0.55 mmol), Cu(I) thiophene-2-carboxylic acid (114 mg, 0.60 mmol) and $Pd(PPh_3)_4$ (5 mg, 10 mol%) in THF (30 mL) under argon atmosphere was stirred for 18 h at 50 °C. The mixture was cooled and then diluted with ether (50 mL). The organic phase was washed with a saturated $NaHCO_3$ solution (50 mL), brine (50 mL) and water (50 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Purification with column chromatography (silica gel, CH_2Cl_2) furnished pure **12** (170 mg, 70%) as a red powder. δ_{H} (300 MHz, DMSO): 3.30 (s, 3H), 7.57–7.60 (m, 6H), 7.92–7.95 (m, 2H), 8.46–8.49 (m, 2H), 11.22 (s(br), 1H); δ_{C} (75 MHz, DMSO): 29.6, 108.9, 110.4, 127.7, 127.9, 128.1, 129.0, 129.3, 129.7, 131.1, 132.4, 146.1, 146.4, 161.8, 162.7; LR-MS (CI): 303 MH^+ .

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