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ARTICLE TYPE

9-Iodophenalenone and 9-Trifluoromethanesulfonyloxyphenalenone: Convenient Entry Points to New Phenalenones Functionalised in 9-Position. Iodine-Carbonyl Interactions Studies by X-Ray Crystallography

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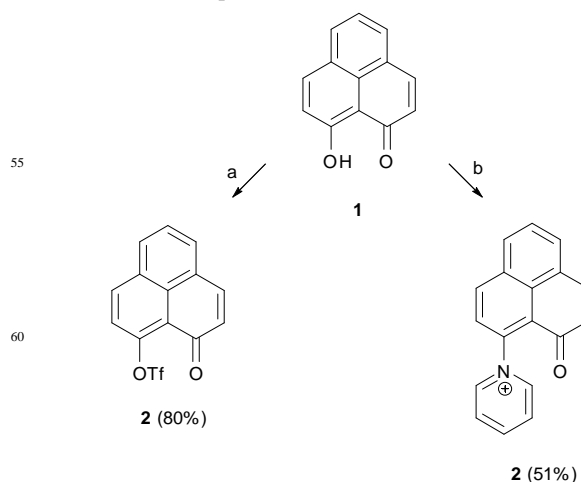
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Reaction of 9-hydroxyphenalenone **1** with triflic anhydride allows access to 9-trifluoromethanesulfonyloxyphenalenone **2**. The reactivity of **2** is explored in the reactions with pyridine, iodide, and azide. Structural aspects of **4**, including carbonyl-iodine interactions, are investigated by X-ray crystallography. Both **2** and 9-iodophenalenone **4** are expected to be valuable precursors in the synthesis of further 9-functionalised phenalenones.

1*H*-Phenalen-1-one (PN) is an aromatic ketone acting as a photosensitizer with a very high singlet oxygen quantum yield of $\Phi \sim 1.0$.^{1,2} As singlet oxygen is a potent antimicrobial agent, derivatives of PN thus have been known to have an important biological function in the self-defense of certain plant species, acting as phytoalexins.^{3,4,5} Beyond that, 9-aryl-substituted PN have been known to serve as biosynthetic precursors to plant dyes of the naphthoxanthone type.^{6,7} Therefore, an alternative synthetic protocol for PN derivatives, in particular for 9-substituted PN, is important. Grignard reagents undergo an atypical Michael-type addition to PN at the 9-C position.⁸ Based on this reaction, a series of 9-aryl-PN have been synthesized.⁹ However, this reaction may result in no success if the desired substituent cannot be transformed into a Grignard reagent, for instance.^{10,11} In terms of material sciences, the functionalization of the parent PN has proven particularly useful in developing new phenalenyl based species aimed towards molecule-based functional materials.¹² This was achieved starting with 9-hydroxy-PN **1**. However, due to the strong intramolecular hydrogen bond between the two oxygen atoms,¹³ **1** first needs to be transformed into a substrate containing a more reactive leaving group. For instance, for the synthesis of Haddon's prototype of an electronically stabilized phenalenyl radical, 1,9-dithiophenalenyl (DTPLY), **1** needed to be transformed to 9-ethoxy-PN.¹⁴ Further advances were made by introducing alkyl and benzylamines which gave access to a series of intriguing phenalenyl based radicals.^{15,16,17} To the best of our knowledge, few derivatives of PN bearing heteroatom substituents in the 9-position have been reported in the literature. With regard to 9-halogenated PN, only

the multistep synthesis of 9-bromo-PN was reported.¹⁸ In this paper, we demonstrate the preparation of 9-trifluoromethanesulfonyloxy-PN **2** and its potential as a new entry point into the chemistry of derivatives of phenalenone functionalised in 9-position.



Scheme 1 Synthesis of **2** and **3**. Reagents and conditions: a) Tf_2O , 30% aq. K_3PO_4 /Toluene (1:1), 0–5°C; b) Tf_2O , Pyridine, rt.

The synthesis of **2** was achieved using K_3PO_4 as a base, slowly adding Tf_2O to a stirring bilayer of a solution of **1** in toluene and 30% aqueous K_3PO_4 solution (Scheme 1).¹⁹ The organic layer was separated and subsequently evaporated till dryness and purified via column chromatography to obtain the yellow product **2** in a yield of 80%. Triflate **2** is stable under air without decomposition. For X-ray quality crystals, **2** could be crystallized as large yellow needles from acetone.

Triflate **2** crystallizes in monoclinic system with space group Cc. The rotational freedom of the triflate group results in a crystal structure involving three different conformations (Fig. 1 and SI). Hence, three unique molecules were found in the asymmetrical unit. Each unique molecule in a symmetric unit cell shows different torsion angles with respect to the two oxygen atoms bond to the phenalenyl skeleton, with values of 7.91°, 10.94° and 14.97°. The internuclear distances between the two oxygen atoms

at the peri positions are about 2.7 Å. Three different conformations can be found which are largely contributed by intermolecular interactions based on the electronegative atoms (O, F) by the triflate group (see SI). Furthermore, short intermolecular contacts are observed such as hydrogen bonding and π - π stacking interactions between the phenalenyl units.

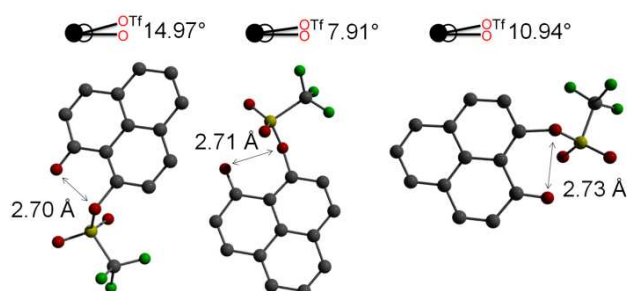
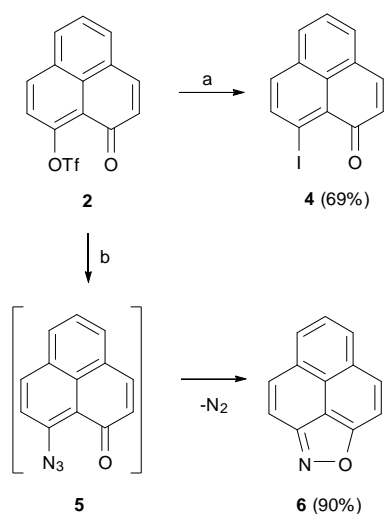


Fig. 1 X-ray structure analysis of compound **2**. Three different conformations are displayed as found in the crystal structure lattice. All molecules are arranged in π - π stacking arrays.

When pyridine was used as a base in the synthesis of **2**, only traces of **2** or recovered starting material were obtained. It was observed that a large amount of material was dissolved in the aqueous pyridine solution which could not be extracted using organic solvents such as ethyl acetate or diethyl ether. The aqueous layer was left to stand in an open beaker overnight in the fumehood. This resulted in the formation of dark brown needles which were separated by filtration yielding compound **3** in almost pure form.



Scheme 2 Synthesis of **4** and **6** resulting from rapid thermolytic cyclization of **5**. Reagents and conditions: a) KI, DMF, heat; b) NaN_3 , DMF, rt.

When **3** was recrystallized from acetone, yellow needles were obtained. According to the X-ray structure analysis, acetone molecules were incorporated in the crystal lattice (see SI). While it appears plausible to assume that **3** is formed by reaction of triflate **2** with pyridine, we note that **2** did not react with pyridine, even when refluxed in the neat base. A possible explanation would be that activation of **2** by reaction with Tf_2O (yielding a 1,9-bis-triflate substituted phenalenyl cation) is required for the reaction to occur. In fact, **3** could be isolated in 36% yield, if **2**

was refluxed in pyridine in the presence of 1 eq. Tf_2O .

4 could be conveniently synthesized via nucleophilic aromatic substitution using **2** as a precursor. The reaction was carried out using 1.0 eq. of **2** with 5 eq. of KI in DMF at 80°C, giving the desired compound **4** in a yield of 69% after column chromatography. **4** was recrystallised from acetone giving dark orange crystals with good quality for X-Ray structure analysis. **4** crystallises in monoclinic system with space group $C2/c$ (see Fig. 2 and SI). One molecule is in the asymmetric unit and all carbon atoms in the molecule are co-planar.

The carbon-oxygen and carbon-iodine bond lengths are $d_{\text{O-C}} = 1.221(7)$ and $d_{\text{C-I}} = 2.111(4)$ Å with an O-C...C-I torsion angle of 9.37°. The internuclear distance between the iodine and oxygen atoms is 3.00 Å, which is well below the sum of the van der Waals radii of iodine and oxygen (3.55 Å). Weak intermolecular contacts are observed including: O...H-C hydrogen bonding, π - π stacking interactions and I...I interactions ($d_{\text{I...I}} = 3.81$ Å).

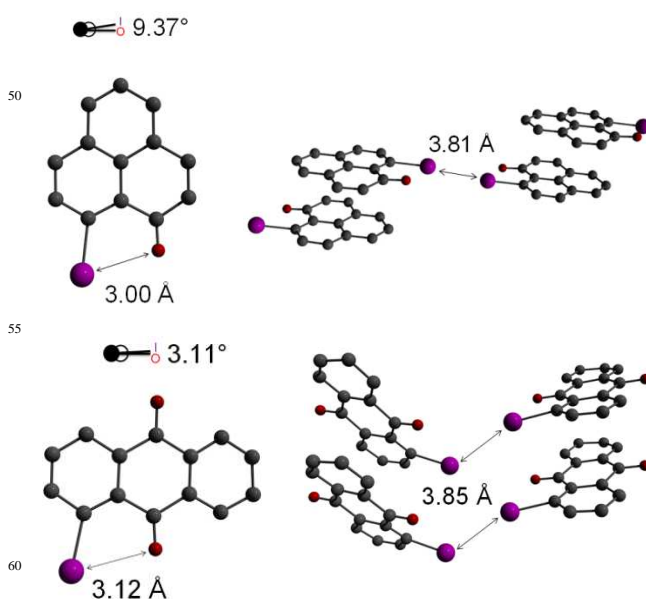


Fig. 2 X-ray diffraction of **4** and 1-iodo-9,10-anthraquinone showing an internuclear distance of 3.00 Å and 3.12 Å, concomitant with a torsion angle of 9.37° and 3.11° between O...I, respectively. Intermolecular separations are similar with 3.81 Å and 3.85 Å between I...I, respectively.

A search for similar systems in the Cambridge Crystallographic Database yielded the structure of 1-iodo-9,10-anthraquinone (see Fig. 2).²⁰ Here, the O...I distance is slightly longer with 3.118 Å, while the OC...CI torsion angle is smaller with 3.1°. The intermolecular I...I distance in 1-iodo-9,10-anthraquinone is 3.850 Å. Comparing **4** and **7**, it thus appears that **4** minimizes unfavourable iodine-oxygen interaction by torsional distortion of the molecular skeleton, whereas **7** prefers widening of the I-C-C and O-C-C angles. We note that computational models give diverging results for **4**. While semi-empirical AM1 theory²¹ predicts torsional distortion as well (torsion angle 20.23°, with an O...I distance of 3.119 Å), the hybrid M05-2X²² or M06 functionals²³ in combination with an SDD²⁴ basis set give a completely planar PN system, with the stretching of the oxygen-iodine distance exclusively achieved by widening of the C-C-I and C-C-O angles.

The electronic absorption spectra of **2** and **4** differ significantly (see Fig. 3). As a comparison, the UV spectrum of parent PN is depicted indicating the $\pi\text{-}\pi^*$ and $n\text{-}\pi^*$ electronic transitions at 357 nm and 380 nm, respectively.²⁵ PN was prepared in our laboratory according to a reported procedure.⁹ The UV/Vis spectrum of **2** is similar to that of PN, hence the triflate substituent appears to have only slight effects on the transitions of the PN chromophore. Compound **4** revealed a red shift of 8 nm with a peak at 365 nm comparing with the absorption peak representing the $\pi\text{-}\pi^*$ transition of PN. In addition, the absorption intensity of the slope indicating the $n\text{-}\pi^*$ transition is distinctly reduced.

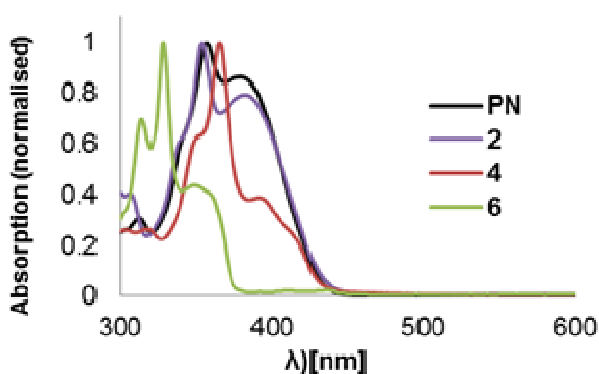


Fig. 3 Normalized UV spectra of PN, **2**, **4** and **6** between 300-600 nm in acetonitrile at room temperature.

We also attempted the synthesis of **5**. However, treatment of **1** with sodium azide in DMF at ambient temperature instead directly gave the isoxazole **6** in a yield of 90% (Scheme 2).²⁶ Hence, azide **5** appears to be unusually labile, dediazotising very easily. The stability of aryl azides has been reported to be strongly linked with the stability of the products (singlet nitrene or rearranged product) formed, with fast dediazotation observed when stable rearranged products are formed in a concerted reaction. Thus, the rate of thermal decomposition of 2-azidothiophene (ring-opening to a nitrile product) has been reported to be 69000 times higher than the rate of thermal decomposition of azidobenzene.^{27,28} The apparent very limited stability of **5** therefore does not surprise. Calculations (M06/cc-pVTZ)²⁹ indicate that the activation enthalpy for conversion of **5** into **6** is only $\Delta H^\ddagger = 27.3$ kcal mol⁻¹, if solvation by DMF is accounted for employing a polarisable continuum model.³⁰ Using CCSD(RHF)/cc-pVTZ(COSMO,DMF)³¹⁻³³ single point energy calculations (ORCA) based on the M06/cc-pVTZ(pcm,DMF) geometries, an electronic activation energy of $\Delta E^\ddagger = 24.3$ kcal mol⁻¹ is computed, whereas CCSD(UHF)/cc-pVTZ(pcm,DMF) // M06 (pcm,DMF)/cc-pVTZ (Gaussian) gives an even smaller $\Delta E^\ddagger = 19.9$ kcal mol⁻¹. At the M06/6-31+G(d,p) level of theory, the activation enthalpy for reaction of **2** with azide, in DMF, is obtained as $\Delta H^\ddagger = 7.8$ kcal mol⁻¹. In comparison, the activation enthalpy for the reaction of **2** with chloride in DMF (to yield 9-chlorophenalenone) is calculated to be higher with $\Delta H^\ddagger = 23.4$ kcal mol⁻¹. As the barrier for thermal decay of **5** is considerably larger than the remarkably small barrier for reaction of **2** with azide, **5** should in principle build up in solution. Based on the calculated (CCSD) energy of activation in combination with the calculated (M06) entropy of activation, the solution lifetime

(DMF) of **5** at $T = 298$ K can be estimated as $\tau \sim 33$ h (CCSD(RHF)) or $\tau \sim 70$ s (CCSD(UHF)).³⁴ Hence, the activation parameters calculated for the cyclisation of **5** indeed indicate that this azide might be too unstable to be isolated at ambient temperature.

Crystals of **6** suitable for X-ray structure analysis could be obtained from acetone.

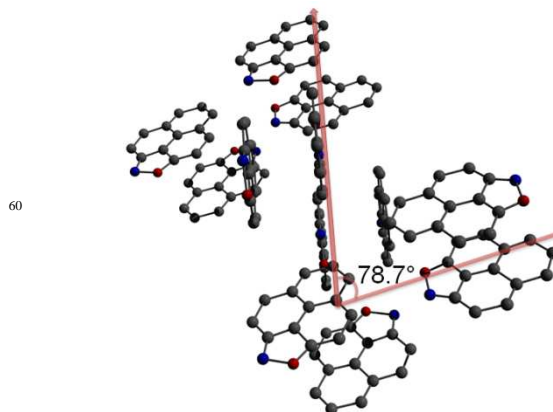


Fig. 4 X-ray diffraction solution of compound **6** showing $\pi\text{-}\pi$ stacking arrays arranging in a dihedral angle of 78.7° .

They form a triclinic system with space group P-1. The unit cell contains four molecules with two being unique in the asymmetrical unit. The O-N groups in both molecules are disordered over two positions with half occupancy each. In this case, Fig. 4 shall depict the most reasonable occupancy of nitrogen and oxygen atoms bond to the phenalenyl unit. The fully planar molecules establish weak $\pi\text{-}\pi$ stacking arrays in an antiplanar manner. These arrays are situated with a cross angle of 78.7° . Moreover, short intermolecular contacts are O...H-C (2.54 & 2.60 Å) and N...H-C (2.66 & 2.49 Å) hydrogen bonding.

The UV/Vis spectrum of **6** shows intense peaks at $\lambda = 314$, 328, and 350 nm, in addition to very weak absorption in the range between $\lambda = 400$ and 500 nm. The double band at $\lambda = 314$ and 328 nm is reproduced by a calculated UV/Vis spectrum (TD-B3LYP/6-31+G(d,p)//M06/6-31+G(d,p), solvation by acetonitrile), where the longest-wavelength absorption is due to $(\pi \rightarrow \pi^*)$ transitions ($\lambda_{\text{max,calc}} = 310, 338$ nm). However, neither the broad band at $\lambda = 350$ nm nor the weak band between $\lambda = 400$ and 500 nm is reproduced by the TD-DFT calculation of an isolated molecule of **6**. Calculations (also TD-B3LYP/6-31+G(d,p)//M06/6-31+G(d,p)) on six different π -dimers of **6** showed that the 350 nm band in the UV/Vis spectrum of **6** could in fact be due to dimer formation, as an intense band in this range is predicted for the dimers (for the calculated spectra, see Supplementary Information). The calculations on the dimers also predict weak to medium intensity bands at around $\lambda = 400$ nm, which could potentially be assigned to the very broad and weak band observed at $\lambda > 400$ nm. We also performed an optimisation of one of the possible π -trimers of **6**. The calculated UV/Vis spectrum of the trimer, however, indicates only a small bathochromic shift, compared with the dimers. As the entropy of formation of the trimer is unfavourable, it is not expected to be present in significant concentrations. As the band between $\lambda =$

400 and $\lambda = 500$ nm is very weak, however, it is conceivable that at least its long-wavelength wing might be due to trimers or even higher aggregates of **6**.

Conclusions

Triflate **2** proved to be a valuable precursor for the synthesis of derivatives of phenalenone functionalised in 9-position. The functionalization of PN with iodine and triflate should make it possible to employ modern palladium chemistry in the quest for new 9-substituted phenalenones with photochemical properties inducing antimicrobial activity or new phenalenyl-based functional materials. Further work in our group will focus on these aspects.

Notes and references

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†Electronic Supplementary Information (ESI) available: Characterization data, including ^1H , ^{13}C and ^{19}F (in the case of compound **1**) NMR spectra. Detailed synthetic protocols. Detailed data of X-ray structure analyses. Cartesian coordinates and energies of stationary points optimised. Calculated UV/Vis spectra. Details of computational methodology used.

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