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Aromatic annulation strategy for naphthalenes fused at 1,2- and 3,4-positions with two heterocycles†

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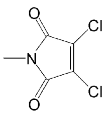
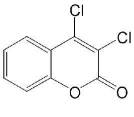
An efficient regioselective naphthoannulation strategy able to fuse a newly formed naphthalene ring at its 1,2- and 3,4-positions to two different heterocycles has been developed.

Selective synthesis of functionalized polycyclic heteroaromatic compounds by annulation methods[1] has been an important task in organic synthesis because polycyclic heterocycles are closely associated with a variety of natural products and unnatural synthetic targets of biological importance, and play an important role in developing new organic electro-optical materials.[2] In this respect, radical cyclization[3] and electrocyclic reaction[4] are among the most powerful and versatile tools. We report here a simple and efficient naphthoannulation strategy[5] starting from photoreactions of *N*-methyl-3,4-dichloromaleimide (**1**) and 3,4-dichlorocoumarin (**2**) with phenyl-substituted heterocycles such as 2- and 3-phenylbenzofurans and 2 and 3-phenylbenzothiophenes **3a**–**3d** which involves radical cyclization and tandem electrocyclic reactions.



1



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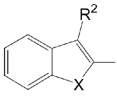
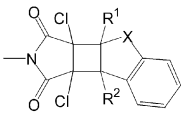
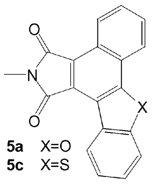


3a-3d

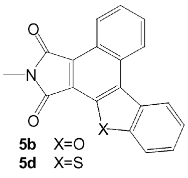


4a-4d

a X=O, R^1=Ph, R^2=H **b** X=O, R^1=H, R^2=Ph
c X=S, R^1=Ph, R^2=H **d** X=S, R^1=H, R^2=Ph



5a X=O
5c X=S



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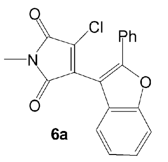
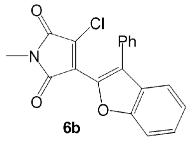
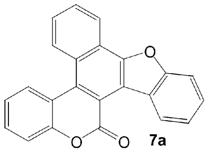
5d X=S



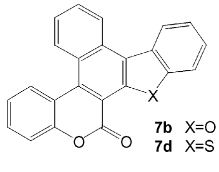
6a



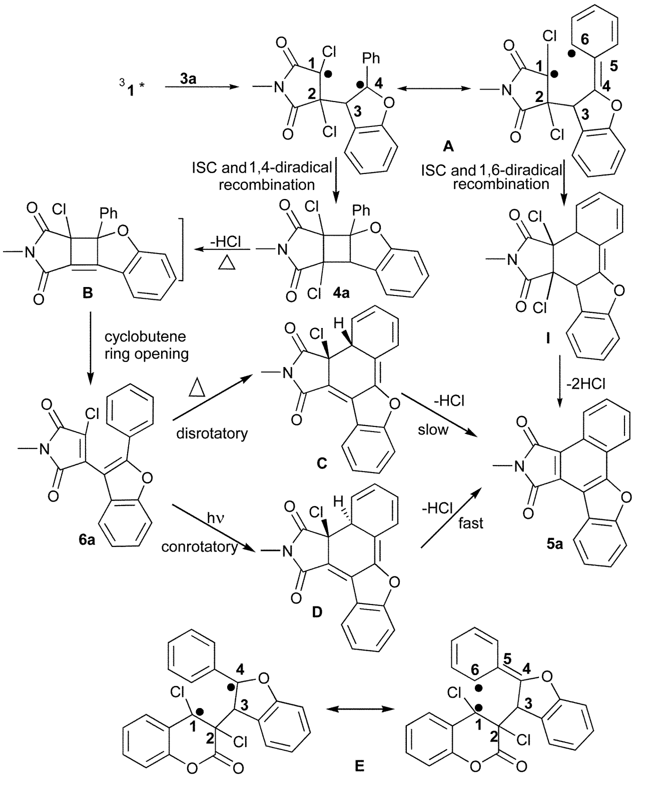
6b



7a



7b X=O
7d X=S



Scheme 1

Irradiation of **1** with **3a** in benzene gave **4a** (73%) and **5a** (24%). While **4a** is a normal [2 + 2] cycloadduct between triplet excited **1** (^{3}**1***) and **3a**, **5a** can be viewed as derived from a formal Diels–Alder adduct **I** (Scheme 1) between **1** and **3a** by eliminating two HCl molecules. However, a control experiment showed that **5a** could not be formed by thermal reactions of **1** with **3a** in the dark either at ambient temperature or at elevated temperature by prolonged refluxing in toluene. Similar irradiation of **2** with **3a** afforded the annulation product **7a** in 58% yield. A cyclobutane product was not found in this case (Table 1). We further found that **4a** can be transformed to **5a** in high yield by first heating on silica gel at 100 °C to give the cyclobutane ring-opening product **6a** (94%) and **5a** (1%), and then irradiating **6a** in acetone solution to give **5a** (96%). As a result, the total yield of **5a** in the photoreaction and subsequent conversion of **4a** is 94%. The mechanism for the formation of **5a** in the photoreaction of **1** with **3a** and by the conversion of **4a** is proposed in Scheme 1.

Addition of ^{3}**1*** with **3a** leads to the diradical intermediate **A** in which the unpaired electron at C4 is delocalized to the *o*- and *p*-carbon atoms in the phenyl ring. Then 1,4- and 1,6-diradical recombination after intersystem crossing (ISC) to singlet manifold gave **4a** and **5a**, respectively. Heating **4a** absorbed on silica gel results in the elimination of hydrogen chloride to afford the thermally labile cyclobutene **B** which underwent electrocyclic ring-opening to give **6a**.[6] Subsequent 6π electrocyclization[7] of **6a** can be achieved thermally or photochemically. As mentioned above, thermal transformation of **6a** to **5a** is very sluggish and by heating **4a** on silica gel for 10 h, only 1% yield of **5a** is formed. On the other hand, irradiating **6a** in acetone led to smooth transformation to

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† Electronic supplementary information (ESI) available: general experimental procedures and analytical data for all products. See DOI: 10.1039/b514496e

Table 1 Synthesis of **5** and **7**

Photoreaction				Conversion of **4**	
Reactants	Irradiation time/h	Conversion (%)	Products and yield (%)	Products and yield (%)	Total yield of **5** and **7** (%)[a]
1, **3a**	21	100	**4a** (73), **5a** (24)	**5a** (92)	**5a** (94)
1, **3b**	48	63	**4b** (87), **5b** (6)	**5b** (95)	**5b** (89)
1, **3c**	27	79	**4c** (84), **5c** (7)	**5c** (94)	**5c** (87)
1, **3d**	44	95	**4d** (75), **5d** (8)	**5d** (86)	**5d** (72)
2, **3a**	48	43	**7a** (58)		**7a** (58)
2, **3b**	48	36	**7a** (71)		**7b** (71)
2, **3c**	Slow reaction[b]				
2, **3d**	72	36	**7d** (67)		**7d** (67)

[a] Total yield of isolated products in the photoreaction and conversion of **4**. [b] Not further investigated.

5a in high yield (96%). These results are attributed to the fact that thermal disrotatory ring-closure in **6a** gave product **C** where H and Cl atoms are in a *cis*-configuration, making their elimination difficult and driving the reversible eletrocyclization backward to the ring-opening form **6a**. At the same time, photoinduced conrotatory ring-closure gave **D** with the H and Cl atoms *trans*- to each other for facile elimination to give product **5a**. A key point to the success of the conversion of **4a** to **5a** is the feasibility of **4a** to eliminate a hydrogen chloride when heating on silica gel. This is because **4a** has a sterically less hindered *anti*-configuration for the pyrroledione and the benzofuran moieties so that the H and Cl atoms are *trans*- to each other, favoring the elimination. This is substantiated by an X-ray crystallographic analysis of **4a**‡ (Fig. 1).

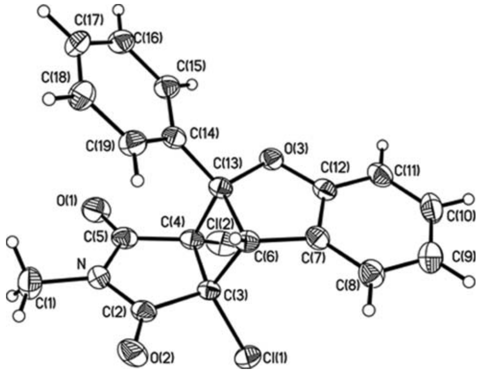

Fig. 1 X-Ray structure of **4a**.

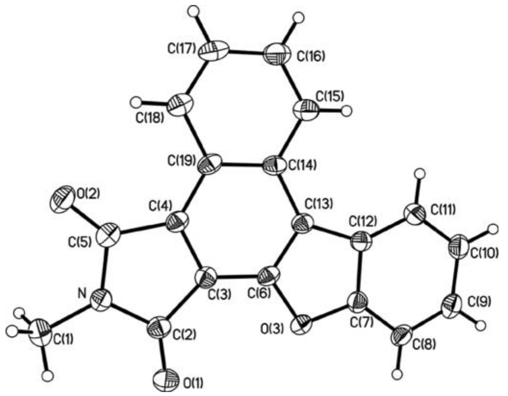

Fig. 2 X-Ray structure of **5b**.

The competition of 1,4- and 1,6-diradical recombination pathways in the diradical intermediates **A** and **E** (Scheme 1) are likely decided by spin distribution and steric hindrance in the two ring-closure modes. Density functional theory (DFT) calculations at the UB3LYP 6-31G level[8] of **A** and **E** reveal that both in the optimized geometry and in conformations suitable for rapid ISC and bond formation,[9] not only do the two radical center C atoms (C1 and C4) have a large spin density, but the *o*- and *p*-carbon atoms in the phenyl ring also share significant spin density to allow direct 1,6-cyclization to the annulation products **5a** and **7a**.

Irradiation of **1** with **3b** furnished **4b** (87%) and **5b** (6%). Heating **4b** on silica gel at 90 °C for 12 h resulted in complete conversion of **4b** and gave **6b** in 96% yield. Photolysis of **6b** gave **5b** in 99% yield. Therefore, the yield of **5b** covering photoreaction and further conversion of **4b** is 89%. The structure of **5b** was also confirmed by an X-ray crystallographic analysis§ (Fig. 2). Similar to the photoreactions of **2** with **3a**, irradiation of **2** with **3b** gave the annulation product **7b** as the only isolable product in 71% yield.

This annulation protocol was also performed for 2- and 3-phenylbenzothiophenes **3c** and **3d**. The results are in Table 1.

Therefore, this naphthoannulation strategy is highly regioselective and high yielding, leading to the simple (sometimes stratightforward) synthesis of polycyclic heterocycles in which coumarin or maleimide (at their 3,4-position) and benzofuran or benzothiophene (at their 2,3-position) are fused at the 1,2- and 3,4-positions of a newly formed naphthalene ring, respectively. Regiochemistry in the annulation product can be controlled simply by changing the position of the phenyl group in the benzofuran and benzothiophene rings.

Aromatic annulated furans,[10] polycyclic thiophene derivatives,[11] 3,4-disubstituted and annulated maleimides[12] and angularly fused polycyclic coumarin derivatives[13] are of current research interest in view of their biological, optical and electrochemical properties, and their syntheses have drawn much attention. However, more thorough investigation of these compounds is still hampered by the lack of general and efficient synthetic methods. The naphthoannulation strategy reported here provides a convenient methodology for the synthesis of these polycyclic systems, and these previously unknown polycyclic systems **5** and **7** would be interesting target compounds for the screening of biological activity and optoelectric properties. All of these compounds are bright yellow or yellow-green colored and are strongly fluorescent in the blue region. The light absorption and emitting properties are shown in Table 2.

Table 2 Spectral properties of compounds **5** and **7** in benzene solution

Compound	λ^{ab}_{max}/nm^a	ε_{max} ($\times 10^4$)/L mol^{-1} cm^{-1}	λ^{f}_{max}/nm^b	Φ_f
5a	397	0.70	450	0.41
5b	403	1.15	455	0.63
5c	405	0.55	465	0.33
5d	401	1.00	463	0.38
7a	403	2.31	441	0.20
7b	410	1.59	448	0.73
7d	418	0.95	457	0.42

[a] The longest wavelength absorption peak in the electronic spectrum. [b] The emission maximum in the fluorescence spectrum.

Research on further use of this annulation strategy for phenyl-substituted heterocycles other than phenylbenzofurans and phenylbenzothiophenes is in progress.

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Notes and references

‡ Crystal data for **4a**. $C_{19}H_{13}Cl_2NO_3$, $M = 374.20$, colorless block, 0.40 × 0.30 × 0.28 mm, monoclinic $P2_1/c$, $a = 12.895(3)$, $b = 9.910(2)$, $c = 13.175(3)$ Å, $\beta = 90.54(3)°$, $V = 1683.6(6)$ Å^3, $Z = 4$, $\mu = 0.404$ mm^{-1}, $2\theta_{max} = 50°$. A total of 3110 measured reflections and 2971 independent reflections were measured at $T = 293(2)$ K. R_{int} and final R are 0.0426 and 0.0536. CCDC reference number 280979. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b514496e.

§ Crystal data for **5b**. $C_{19}H_{11}NO_3$, $M = 301.29$, yellow needles, 0.40 × 0.30 × 0.24 mm, monoclinic $P2_1/c$, $a = 9.5260(19)$, $b = 18.319(4)$, $c = 7.9420(16)$ Å, $\beta = 96.25(3)°$, $V = 1377.7(5)$ Å^3, $Z = 4$, $\mu = 0.099$ mm^{-1}, $2\theta_{max} = 50.14°$. A total of 2629 measured reflections and 2439 independent reflections were measured at $T = 293(2)$ K. R_{int} and final R are 0.0433 and 0.0551. CCDC reference numbers 280980. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b514496e.

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