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Synthesis of novel azaxanthones derived from *N*-hydroxyazoles

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Abstract—The synthesis of a new class of azaxanthones is presented. The *N–O* functionality of 1-hydroxypyrazole and 1-hydroxy-1,2,3-triazole was used to direct metalation and subsequently incorporated in the new ring systems. © 2002 Published by Elsevier Science Ltd.

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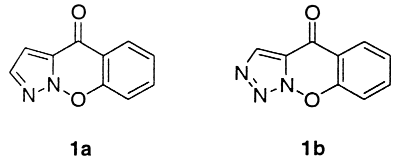
1. Introduction

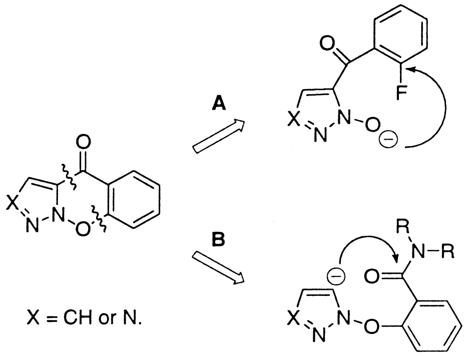
The regioselective functionalisation of 1-hydroxypyrazole and 1-hydroxy-1,2,3-triazole was reported recently.[1–4] We sought to incorporate the *N–O* functionality in a new and distinct group of heterocyclic systems using these protocols. The xanthone is an ubiquitous structural motif found in numerous natural products, and substituted derivatives have a broad spectrum of biological activities.[5–10] The azaxanthones **1a** and **1b** in Scheme 1 were chosen as the target molecules.



Scheme 1. The target azaxanthones.

2. Retrosynthetical analysis

We speculated that the compounds could be prepared via two different approaches, see Scheme 2. In route A, the central ring would be constructed via an intramolecular nucleophilic aromatic substitution. Route B involves an anionic intramolecular ring closure, analogous to the recent synthesis of substituted xanthones reported by Snieckus.[11–13]



Scheme 2. Retrosynthetical analysis. Routes A and B.

3. Synthesis of 1a and 1b—route A

1-(Benzyloxy)pyrazole **2a** and 1-benzyloxy-1,2,3-triazole **2b** were acylated in 82 and 71% yield, respectively via our metalation/transmetalation/cross-coupling protocols, followed by debenzylation, see Scheme 3. The crucial ring closure via displacement of the 2-fluoro substituent proceeded under very mild conditions: treating **4a** and **4b** with 2 equiv. K_2CO_3 in DMF at 50°C for 30 min gave full conversion to the desired azaxhanthones **1a** and **1b**.[14]

Suitable crystals of **1b** were obtained, and an X-ray structure confirmed the structural assignment (Fig. 1).[15]

Although the synthesis proceeds very smoothly it requires four individual steps: benzylation, acylation, debenzylation and ring closure. Thus, a shorter synthesis would be desirable.

When *ortho*-lithiated aryl carbamates are warmed to rt an anionic Fries rearrangement produces the corresponding salicylamides, see Scheme 4.[16] If the lithiated pyrazole **5** depicted in Scheme 4 could be generated, a similar rearrangement would give **4a**, thereby circumventing the

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Keywords: azaxanthones; cyclisations; anionic ring closure.

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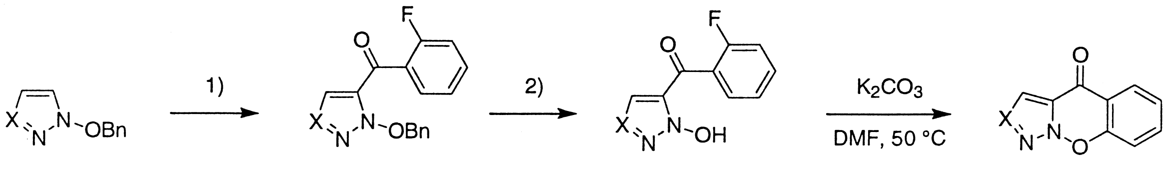


2a, X = CH	**3a**, 82 %	**4a**, 99 %	**1a**, 97 %
2b, X = N	**3b**, 71 %	**4b**, 100 %	**1b**, 98 %

1) See experimental section. 2) **3a**: 37 % HCl, **3b**: H_2/Pd(C), MeOH.

Scheme 3. Synthesis of **1a** and **1b** via route A.

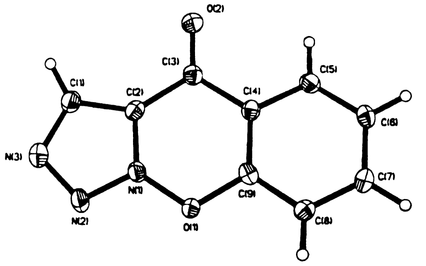
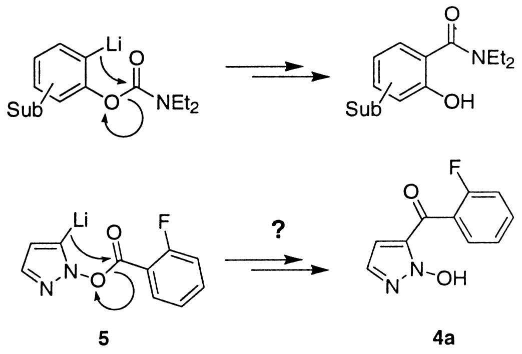


Figure 1. X-Ray structure of **1b**.

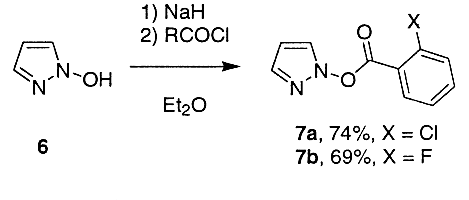
tedious benzylation/debenzylation steps required in the first synthesis.

O-Acylated 1-hydroxypyrazoles have been reported previously,[17,18] and acylation of **6** gave **7a** and **7b** isolated in 74 and 69% yield, respectively, see Scheme 5. 1-Hydroxy-1,2,3-triazoles have been reported as very active analogues of *N*-hydroxybenzotriazoles in peptide coupling reactions, so we speculated that the *O*-acylated triazole derivatives would be too unstable to be isolated.[19]

The generation of the anion **5** was hampered by competing nucleophilic attack of the base on the ester-carbonyl. A series of bases were tested (*t*-BuLi, LDA, LiTMP, $(TMP)_2Mg$[20]) but yields were low, 5–25% after subsequent ring closure to **1a**. The isolated yields were slightly higher when **7a** was used instead of **7b**.

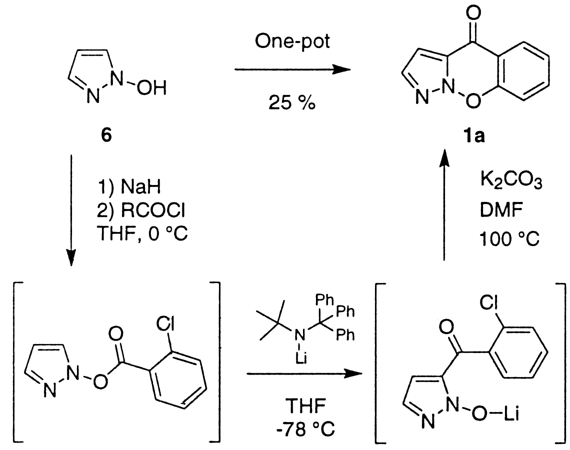


Scheme 4. Possible anionic Fries rearrangement giving **4a**.



Scheme 5. Synthesis of *O*-acyl 1-hydroxypyrazoles **7a** and **7b**.

The best overall yield (25%) was obtained when the three step sequence **6** to **1a** was performed one-pot, using the very hindered base lithium *t*-butyltritylamide,[21] see Scheme 6. Although the yield is modest, it represents a very fast way of accessing **1a**.



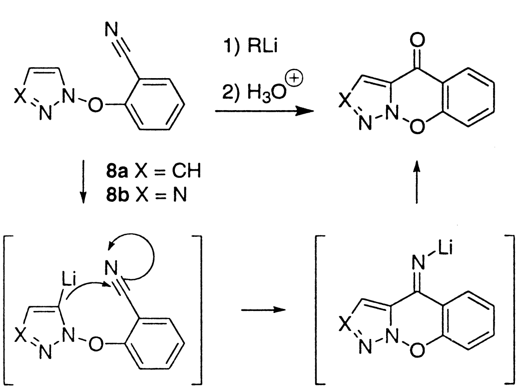
Scheme 6. One-pot synthesis of **1a** from **6**.

4. Synthesis of 1a and 1b—route B

Next, we focused on the development of route B, see Scheme 2. However, all attempts to prepare the required *O*-arylated *N*-hydroxyazoles using the procedure developed by Snieckus for the synthesis of diaryl ethers were unsuccessful.[22] Nevertheless, the concept of constructing the *O*-aryl bond prior to ring closure remained attractive, as this would shorten the synthesis. Compounds **8a** and **8b** were chosen as substrates for a modified version of the Snieckus protocol, see Scheme 7.

The ease with which **2a** and **2b** is lithiated, suggested that **8a** and **8b** could be lithiated in the 5-position under comparably mild conditions, thus generating the anion required for the ring closure.

The activating power of the cyano group in nucleophilic

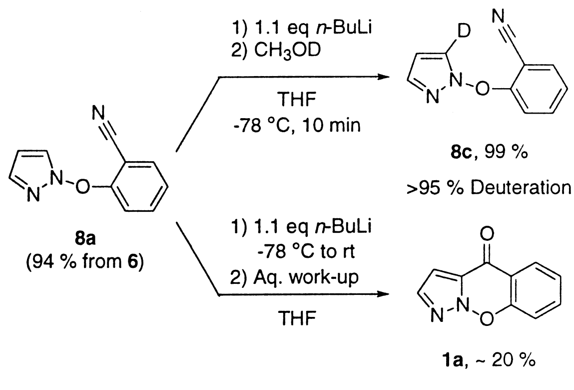


Scheme 7. Proposed new anionic ring closure.

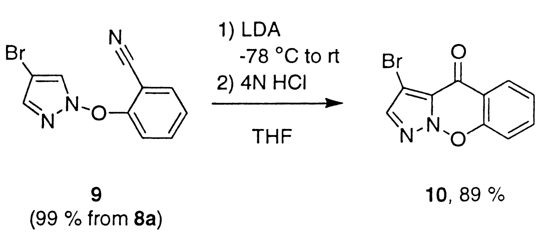
aromatic substitution is well documented.[23–25] Consequently, stirring the Na-salt of **6** with 2-fluorobenzonitrile in DMF for 3 h at 70°C gave **8a** in 94% yield. Surprisingly, 1-hydroxy-1,2,3-triazole failed to give the desired product **8b** under similar conditions.

Treating **8a** with 1.1 equiv. *n*-butyllithium in THF at −78°C for 10 min, followed by quench with CH_3OD gave **8c** with >95% deuterium incorporation at C-5, see Scheme 8. This showed that the required anion could be generated, and the ring closure was attempted.

After lithiation at −78°C, the reaction was warmed to rt. Judged from TLC, full conversion of **8a** to a single more polar compound had occurred. Addition of 4N HCl produced the desired compound **1a**, but the hydrolysis was accompanied by the formation of an insoluble precipitate and the isolated yield of **1a** was low. Repeated efforts using different bases and work up procedures gave isolated yields around 20%. Simply adding water to the presumed imin-anion induced precipitation, and all efforts to circumvent this problem were unsuccessful.



Scheme 8. Lithiation and ring closure of **8a**.



Scheme 9. Ring closure of **9** to **10**.

This precipitation was not observed when a substituent was present at C-4. The 4-bromo derivative **9**, prepared in 99% from **8a**, gave the desired azaxanthone **10** in 89% yield, see Scheme 9. To avoid halogen–metal exchange, LDA was used as base in the lithiation/ring closure step.

5. Synthesis of functionalised derivatives of 1a

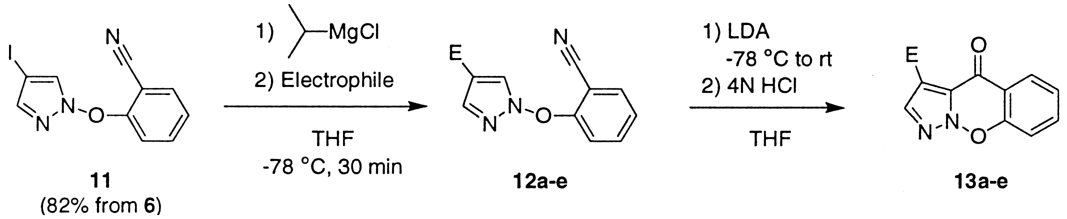
Inspired by our previously reported synthesis of 4-substituted 1-(benzyloxy)pyrazoles via iodine-magnesium exchange of 4-iodo-1-(benzyloxy)pyrazole, we investigated the synthesis of substituted derivatives of **1a**.[3] The 4-iodopyrazole **11** was obtained in 82% yield over two steps from **6**. Iodine–magnesium exchange with *i*Pr-MgCl at −78°C and quenching with CH_3OD after 30 min gave **8a** with ~95% deuterium incorporation at C-4. A small series of electrophiles was introduced using this protocol, see Table 1.

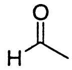
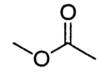
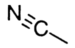
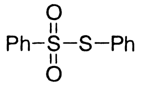
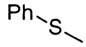
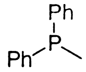
When the magnesiated intermediate was treated with methyl-, ethyl-, benzyl chloroformate or with diethyl glyoxylate complex mixtures were obtained and the isolated yields were low. Addition of copper- or manganese salts did not improve the yields. Methyl cyanoformate is an effective reagent for the C-acylation of lithium enolates.[26] Using this reagent as electrophile, the desired compound was isolated in 94% yield. In the synthesis of **12d** the use of $PhSO_2SPh$ was crucial, as the isolated yield dropped below 30% with PhSSPh as electrophile. TMS-Cl and TBDMS-Cl did not react even after prolonged stirring at rt.

The cyclisations of the functionalized compounds were met with mixed success. Pyrazoles **12a** and **12b** gave complex mixtures, whereas **12c** and **12d** yielded the desired 4-substituted azaxanthones **13c** and **13d** in 82 and 79% yield, respectively. The intermediate Ph_2P-derivative **12e** was very sensitive to oxygen, and it was found that the sequence **11**→**12e**→**13e** could be performed one-pot giving **13e** in excellent yield. Performing the sequence **11**→**12c**→**13c** and **11**→**12d**→**13d** in a similar one-pot fashion gave lower overall yields.

Extension of this approach to the synthesis of aryl-substituted analogous was examined. Transmetalation of the magnesiated intermediate with $ZnCl_2$ and subsequent Pd(0) catalyzed cross-coupling with 4-iodotoluene gave the desired compound **14** in 80% after 18 h at rt, see Scheme 10. The following ring closure produced **15** in 91% yield. In the coupling of **11** to **14** an appreciable amount of 2-hydroxybenzonitrile was also formed, presumably via cleavage of the N–O bond in either **11** or **14**. Efforts toward synthesizing other 4-aryl-substituted derivatives were plagued by this side reaction, thus the reaction is of limited scope. Moreover, efforts to synthesize **14** via Suzuki–Miyaura cross-coupling[27] of either **9** or **11** with 4-tolylboronic acid gave low yields of **14**, and also led to the formation of 2-hydroxybenzonitrile—clearly indicating the sensitive nature of the N–O bond.

Table 1. Introduction of electrophiles followed by ring closure



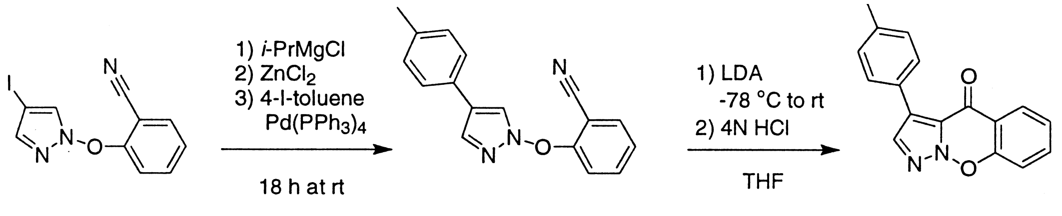
Entry	Electrophile	E	Compound	Yield (%)	Compound	Yield (%)
1	DMF		**12a**	65	**13a**	–[a,b]
2	$NCCOOCH_3$		**12b**	94[c]	**13b**	–[b,d]
3	TsCN		**12c**	86	**13c**	82
4	 $Ph-S(=O)_2-S-Ph$		**12d**	93	**13d**	79
5	$ClP(Ph)_2$		**12e**	Not isolated	**13e**	98 over 2 steps

[a] 3 equiv. LDA was used.

[b] Very complex mixture as judged from TLC and ^1H NMR. No attempt to isolate any product was made.

[c] Isolated as a 15:1 mixture of **12b** and **8a** after FC.

[d] LiTMP was used instead of LDA.



11 14, 80 % 15, 91 %

Scheme 10. Negishi cross-coupling followed by ring closure.

6. Conclusion

A novel anionic ring closure to construct a new class of azaxanthones has been described. We are currently investigating the scope of this reaction for the preparation of other heteroaryl- and arylxanthones.

7. Experimental

7.1. General

All reactions involving air- and moisture sensitive reagents were performed under N_2 using syringe-septum cap technique. All glassware was flame-dried under vacuum prior to use. THF was distilled from Na/Benzophenone. DMF was sequentially dried and stored over 3 Å sieves. All other chemicals were used as received from commercial suppliers. 1-Hydroxypyrazole **6** was prepared as previously described.[28] Melting points are uncorrected. NMR spectra were recorded on a 300 MHz Varian instrument using $CDCl_3$ as solvent with TMS as internal standard, unless otherwise noted. The multiplicity of ^{13}C signals are assigned based on APT spectra, and ppm values are given relative to the solvent peak ($CDCl_3$=76.9 ppm).

7.1.1. 5-(2-Fluorobenzoyl)-1-(benzyloxy)pyrazole (3a). Prepared form 1-(benzyloxy)pyrazole (**2a**) and 2-fluorobenzoyl chloride as described in Ref. 2. 400 mg **2a** yielded 556 mg (82%) **3a** as a colourless oil, R_f (heptane/EtOAc 5:1) 0.38. ^1H NMR ($CDCl_3$): 5.40 (s, 2H), 6.39 (d, 1H, J=2.4 Hz), 7.28–7.46 (m, 10H). ^{13}C NMR ($CDCl_3$): 81.3 (t), 110.2 (d(d), J_{C-F}=2 Hz), 116.4 (d(d), J_{C-F}=22 Hz), 124.0 (d(d), J_{C-F}=4 Hz), 126.4 (s(d), J_{C-F}=13 Hz), 128.5 (d), 129.3 (d), 130.0 (d), 130.7 (d(d), J_{C-F}=2 Hz), 132.2 (d), 132.9 (s), 133.6 (s), 134.0 (d(d), J_{C-F}=9 Hz), 160.4 (s(d), J_{C-F}=256 Hz), 180.2 (s). Anal. calcd for $C_{17}H_{13}FN_2O_2$: C, 68.91; H, 4.42; N, 9.45. Found: C, 68.95; H, 4.45, N, 9.36.

7.1.2. 5-(2-Fluorobenzoyl)-1-hydroxypyrazole (4a). 3a (374 mg, 1.26 mmol) was suspended in 37% HCl (5 mL) and heated to 70°C for 5 h. The mixture was cooled to rt and transferred to a separating funnel using 37% HCl (3×1 mL). Toluene (1 mL) was added, and the separating funnel was shaken vigorously. The phases were separated and the toluene phase was extracted once with 37% HCl (3 mL). The combined HCl phase was cooled to 0°C and 33% NaOH (6 mL) was added cautiously. Water (10 mL) was added to dissolve the formed precipitate and the aqueous phase was extracted with Et_2O (3×30 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated giving 258 mg (99%) **4a** as white crystals, mp 116°C (heptane/EtOAc), R_f (EtOAc) 0.37. ^1H NMR (Acetone-d_6): 6.69 (t, 1H, J=2.4 Hz), 7.21–7.28 (m, 2H), 7.33 (td, 1H, J=7.6, 1.1 Hz), 7.64 (dddd, 1H, J=15.8, 8.4, 5.1, 1.8 Hz), 7.68–7.74 (m, 2H). ^{13}C NMR (Acetone-d_6): 109.1 (d(d), J_{C-F}=2 Hz), 115.5 (d(d), J_{C-F}=22 Hz), 123.8 (d(d), J_{C-F}=4 Hz), 125.8 (s(d), J_{C-F}=14 Hz), 129.8 (d(d), J_{C-F}=2 Hz), 130.3 (d), 131.0 (s), 133.5 (d(d), J_{C-F}=9 Hz), 159.4 (s(d), J_{C-F}=253 Hz), 180.5 (s). Anal. calcd for $C_{10}H_7FN_2O_2$: C, 58.26; H, 3.42; N, 13.59. Found: C, 58.49; H, 3.62, N, 13.59

7.1.3. 9-Oxa-1,9a-diaza-cyclopenta[*b*]naphthalen-4-one (1a). **4a** (310 mg, 1.50 mmol) and freshly ground K_2CO_3 (414 mg, 3.00 mmol) was suspended in DMF (8 mL) and heated to 50°C for 30 min. Brine (10 mL) and water (10 mL) was added, and the mixture was extracted with Et_2O (3×30 mL). The combined organic phase was washed once with brine (10 mL), dried ($MgSO_4$) and evaporation of the solvent gave 273 mg (97%) **1a** as white crystals, mp 135°C (heptane/EtOAc), R_f (heptane/EtOAc 3:1) 0.41. ^1H NMR ($CDCl_3$): 7.08 (d, 1H, J=2.4 Hz), 7.41–7.49 (m, 2H), 7.57 (d, 1H, J=2.4 Hz), 7.79 (ddd, 1H, J=8.4, 7.2, 1.5 Hz), 8.30 (dd, 1H, J=7.8, 1.5 Hz). ^{13}C NMR ($CDCl_3$): 103.2 (dd, J_{C-H}=185, 10 Hz), 114.4 (dddd, J_{C-H}=166, 8, 3, 1 Hz), 117.8 (dd, J_{C-H}=9, 5 Hz), 124.9 (dd, J_{C-H}=164, 8 Hz), 126.7 (ddd, J_{C-H}=167, 8, 1 Hz), 129.1 (dd, J_{C-H}=9, 5 Hz), 132.4 (dd, J_{C-H}=194, 4 Hz), 135.5 (ddd, J_{C-H}=162, 10, 3 Hz), 156.6 (dddd, J_{C-H}=8.9, 8.6, 4, 2 Hz), 169.5 (d, J_{C-H}=4 Hz). Anal. calcd for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.66; H, 3.35, N, 15.07.

7.1.4. 5-(2-Fluorobenzoyl)-1-benzyloxy-1,2,3-triazole (3b). Prepared form 1-benzyloxy-1,2,3-triazole (**2b**) and 2-fluorobenzoyl chloride as described in Ref. 4. 337 mg **2b** yielded 405 mg (71%) **3b** as white crystals, mp 66–67°C (heptane/EtOAc), R_f (heptane/EtOAc 1:1) 0.60. ^1H NMR ($CDCl_3$): 5.53 (s, 2H), 7.18 (ddd, 1H, J=10.5, 8.7, 0.9 Hz), 7.28 (td, 1H, J=7.5, 1.2 Hz), 7.34–7.42 (m, 5H), 7.49–7.55 (m, 1H), 7.61 (dddd, 1H, J=8.4, 7.2, 5.1, 1.8 Hz), 7.88 (d, 1H, J=1.5 Hz). ^{13}C NMR ($CDCl_3$): 83.5 (t), 116.7 (d(d), J_{C-F}=22 Hz), 124.4 (d(d), J_{C-F}=4 Hz), 125.3 (s(d), J_{C-F}=12 Hz), 128.7 (d), 129.77 (s), 129.84 (d), 130.2 (d), 130.8 (d(d), J_{C-F}=2 Hz), 131.8 (s), 135.1 (d(d), J_{C-F}=9 Hz), 136.6 (d(d), J_{C-F}=3 Hz), 160.6 (s(d), J_{C-F}=257 Hz), 178.5 (s). Anal. calcd for $C_{16}H_{12}FN_3O_2$: C, 64.64; H, 4.07; N, 14.13. Found: C, 64.87; H, 4.14; N, 14.26.

7.1.5. 1-(2-Fluorobenzoyl)-1-hydroxy-1,2,3-triazole (4b). **3b** (305 mg, 1.03 mmol) and 10% Pd(C) (32 mg) was dissolved in MeOH (10 mL) and cooled to 0°C. The flask was fitted with a H_2-ballon and stirring was continued at 0°C for 30 min. The mixture was filtrated through a plug of celite and the solvent was evaporated, giving 212 mg (100%) **4b** as slightly yellow crystals. Recrystallization from MeOH gave white crystals, mp 66–67°C. ^1H NMR (DMSO-d_6): 7.36–7.42 (m, 2H), 7.63–7.76 (m, 2H), 8.24 (s, 1H). ^{13}C NMR (DMSO-d_6): 116.7 (d(d), J_{C-F}=22 Hz), 125.2 (d(d), J_{C-F}=3 Hz), 125.9 (s(d), J_{C-F}=12 Hz), 129.1 (s), 131.0 (d(d), J_{C-F}=2 Hz), 135.4 (d(d), J_{C-F}=9 Hz), 136.4 (s), 160.3 (s(d), J_{C-F}=253 Hz), 179.7 (s). Anal. calcd for $C_9H_6FN_3O_2$: C, 52.18; H, 2.92; N, 20.28. Found: C, 51.92; H, 3.12, N, 20.07.

7.1.6. 9-Oxa-1,2,9a-triaza-cyclopenta[*b*]naphthalen-4-one (1b). Procedure, see **4a** to **1a** above. 73 mg **4b** gave 65 mg (98%) **1b** as white crystals, mp 159–160°C (heptane/EtOAc), R_f (heptane/EtOAc 1:1) 0.55. ^1H NMR ($CDCl_3$): 7.51–7.59 (m, 2H), 7.90 (ddd, 1H, J=9.0, 7.2, 1.8 Hz), 8.31 (dd, 1H, J=7.2, 1.8 Hz), 8.44 (s, 1H). ^{13}C NMR ($CDCl_3$): 114.7 (dddd, J_{C-H}=167, 8, 2, 1 Hz), 118.2 (dd, J_{C-H}=8, 4 Hz), 124.8 (d, J_{C-H}=15 Hz), 126.1 (dd, J_{C-H}=165, 8 Hz), 127.0 (ddd, J_{C-H}=168, 8, 1 Hz), 131.8 (d, J_{C-H}=204 Hz), 136.8 (ddd, J_{C-H}=163, 9, 2 Hz), 156.6 (ddt, J_{C-H}=11, 4, 1 Hz), 168.3 (dd, J_{C-H}=4.0, 1.4 Hz). Anal. calcd for $C_9H_5N_3O_2$: C, 57.76; H, 2.69; N, 22.45. Found: C, 58.04; H, 2.80, N, 22.22.

7.1.7. 1-(2-Chlorobenzoyloxy)-pyrazole (7a). **6** (988 mg, 11.8 mmol) was dissolved in Et_2O (30 mL) under N_2 and cooled to 0°C before NaH (60% in mineral oil, 520 mg, 12.9 mmol) was added in small portions. Stirring was continued at 0°C until the evolution of H_2 ceased (~10 min). 2-Chlorobenzoyl chloride was added and the icebath was removed. Stirring was continued at rt for 30 min, before quenching with sat. $NaHCO_3$ (30 mL). Water was added until two clear phases appeared. The phases were separated, and the aqueous phase was extracted with Et_2O (3×50 mL), drying ($MgSO_4$) and evaporation of the solvent gave the crude product which was purified by FC giving a clear colourless oil. Crystallization from Et_2O/hetane gave 1.92 g (74%) **7a** as white crystals, mp 56–58°C. ^1H NMR ($CDCl_3$): 6.41 (t, 1H, J=2.4 Hz), 7.40–7.47 (m, 2H), 7.49 (dd, 1H, J=2.4, 1.0 Hz), 7.56–7.59 (m, 2H), 8.10 (ddd, 1H, J=7.8, 1.5, 0.6 Hz). ^{13}C NMR ($CDCl_3$): 104.8 (d), 124.1 (d), 124.9 (s), 126.8 (d), 131.5 (d), 132.0 (d), 134.4 (d), 134.5 (d), 135.1 (s), 162.6 (s). Anal. calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 54.20; H, 3.24, N, 12.53.

7.1.8. 1-(2-Fluorobenzoyloxy)-pyrazole (7b). **7b** was prepared using an identical procedure with 2-fluorobenzoyl chloride. 460 mg **6** gave 1.11 g (69%) **7b** as white crystals, mp 61–63°C. ^1H NMR ($CDCl_3$): 6.38 (t, 1H, J=2.4 Hz), 7.22 (ddd, 1H, J=10.7, 8.4, 1.1 Hz), 7.29 (td, 1H, J=7.7, 1.1 Hz), 7.44 (dd, 1H, J=2.3, 1.1 Hz), 7.47 (dd, 1H, J=2.5, 1.0 Hz), 7.66 (dddd, 1H, J=8.4, 7.4, 4.9, 1.8 Hz), 8.07 (ddd, 1H, J=7.6, 7.0, 1.8 Hz). ^{13}C NMR ($CDCl_3$): 104.7 (d), 114.0 (s(d), J_{C-F}=10 Hz), 117.2 (d(d), J_{C-F}=22 Hz), 124.1 (d), 124.4 (d(d), J_{C-F}=4 Hz), 132.3 (d), 134.3 (d), 136.6 (d(d), J_{C-F}=9 Hz), 161.7 (s(d), J_{C-F}=4 Hz), 162.2 (s(d), J_{C-F}=264 Hz). Anal. calcd for $C_{10}H_7FN_2O_2$: C, 58.26; H, 3.42; N, 13.59. Found: C, 58.21; H, 3.42, N, 13.57.

7.1.9. One-pot synthesis of 1a from 6. **6** (120 mg, 1.43 mmol) was dissolved in THF (4 mL) under N_2 and cooled to 0°C before NaH (washed three times with dry pentane immediately prior to use, 38 mg, 1.6 mmol) was added and stirring was continued at 0°C for 10 min before

2-chlorobenzoyl chloride (200 μL, 1.57 mmol) was added. After 45 min at 0°C, the mixture was cooled to −78°C and a freshly prepared solution of lithium *t*-butyltritylamide (1.72 mmol in 3 mL THF) was added.[21] 15 min later the cooling bath was removed and the mixture was warmed to rt. At rt, freshly grinded K_2CO_3 (300 mg, 2.15 mmol) and DMF (2 mL) was added and the mixture was heated to 100°C for 12 h. Cooling to rt and work up as described for **4a** to **1a** gave the crude product which was purified by FC giving 67 mg (25%) **1a** as white crystals, identical to the material described above.

7.1.10. 2-(Pyrazol-1-yloxy)-benzonitrile (8a). NaH (60% in mineral oil, 870 mg, 21.7 mmol) was suspended in DMF (18 mL) under N_2 at rt. 1-Hydroxypyrazole (**6**) (1.52 g, 18.1 mmol) was added in small portions over 5 min. Stirring was continued at rt for 15 min before 2-fluorobenzonitrile (2.16 mL, 19.9 mmol) was added, and the mixture was heated to 70°C. After 3 h, the mixture was cooled to rt and quenched carefully with sat NH_4Cl (20 mL), water (20 mL) was added and the mixture was extracted with Et_2O (4×25 mL). The combined organic phase was dried ($MgSO_4$) and the solvent was evaporated. FC (heptane/EtOAc) yielded 3.14 g (94%) of **8a** as a colourless thick oil that crystallized upon standing, mp 40–41°C (heptane/Et_2O), R_f (heptane/EtOAc 3:1) 0.30. ^{1}H NMR ($CDCl_3$): 6.40 (t, 1H, *J*=2.4 Hz), 6.53 (dd, 1H, *J*=8.7, 0.6 Hz), 7.23 (td, 1H, *J*=7.6, 1.0 Hz), 7.45 (dd, 1H, *J*=2.4, 1.0 Hz), 7.52 (ddd, 1H, *J*=8.7, 7.6, 1.7 Hz), 7.57 (dd, 1H, *J*=2.4, 1.0 Hz), 7.69 (dd, 1H, *J*=7.7, 1.7 Hz). ^{13}C NMR ($CDCl_3$): 100.0 (s), 105.0 (d), 113.4 (d), 114.4 (s), 123.2 (d), 124.6 (d), 133.7 (d), 134.5 (d), 134.5 (d), 160.7 (s). Anal. calcd for $C_{10}H_7N_3O$: C 64.86, H 3.81, N 22.69. Found: C 65.08, H 3.95, N 22.81

7.1.11. 2-(4-Bromopyrazol-1-yloxy)-benzonitrile (9). To a solution of **8a** (647 mg, 3.49 mmol) and freshly ground K_2CO_3 (720 mg, 5.2 mmol) in CH_2Cl_2 (10 mL) at −78°C, Br_2 (0.36 mL, 6.98 mmol) was added dropwise. Stirring was continued for 5 min before the cooling bath was removed. At rt stirring was continued for 30 min before 1N Na_2SO_3 (20 mL) was added. Extraction with CH_2Cl_2 (3×20 mL), drying of the organic phase ($MgSO_4$) and removal of the solvent gave 913 mg (99%) **9** as colourless crystals, mp 87°C (heptane/EtOAc), R_f (heptane/EtOAc 3:1) 0.35. ^{1}H NMR ($CDCl_3$): 6.64 (ddd, 1H, *J*=8.6, 1.0, 0.4 Hz), 7.28 (td, 1H, *J*=7.6, 1.0 Hz), 7.43 (d, 1H, *J*=1.0 Hz), 7.56 (ddd, 1H, *J*=8.6, 7.6, 1.7 Hz), 7.64 (d, 1H, *J*=1.0 Hz), 7.70 (ddd, 1H, *J*=7.7, 1.7, 0.4 Hz). ^{13}C NMR ($CDCl_3$): 92.8 (s), 100.5 (s), 113.8 (d), 114.2 (s), 123.5 (d), 125.2 (d), 133.9 (d), 134.7 (d), 135.3 (d), 160.2 (s). Anal. calcd for $C_{10}H_6BrN_3O$: C, 45.48; H, 2.29; N, 15.91. Found: C, 45.77; H, 2.45, N, 16.01.

7.1.12. 2-(4-Iodopyrazol-1-yloxy)-benzonitrile (11). The procedure described for the preparation of **8a** using NaH (1.50 g, 37.5 mmol), 1-hydroxypyrazole (2.63 g, 31.3 mmol) and DMF (30 mL) was followed. The crude product was dissolved in CH_2Cl_2 (50 mL) and freshly ground K_2CO_3 (8.6 g, 62.6 mmol) was added. ICl (10.8 g, 66.3 mmol) dissolved in CH_2Cl_2 (30 mL) was added to the mixture. The flask was wrapped in alufoil, fitted with a condenser and heated to reflux for 1 h (oil bath at 60°C). After cooling to rt the mixture was quenched with Na_2SO_3 (1 M, 100 mL) and HCl (4N, 20 mL), and extracted with CH_2Cl_2 (3×100 mL). The combined organic phase was dried ($MgSO_4$) and the solvent was evaporated giving the crude product as orange crystals. FC (heptane/EtOAc) yielded 7.98 g (82%) **11** as slightly yellow crystals. Recrystallization from heptane/EtOAc gave 7.08 g (73%) colourless crystals, mp 94–95°C, R_f (heptane/EtOAc 3:1) 0.35 ^{1}H NMR ($CDCl_3$): 6.63 (ddd, 1H, *J*=8.6, 1.0, 0.4 Hz), 7.27 (td, 1H, *J*=7.6, 1.0 Hz), 7.49 (d, 1H, *J*=1.0 Hz), 7.55 (ddd, 1H, *J*=8.6, 7.6, 1.7 Hz), 7.64 (d, 1H, *J*=1.0 Hz), 7.70 (ddd, 1H, *J*=7.7, 1.7, 0.4 Hz). ^{13}C NMR ($CDCl_3$): 55.5 (s), 100.5 (s), 113.8 (d), 114.2 (s), 125.1 (d), 127.3 (d), 133.9 (d), 134.7 (d), 139.7 (d), 160.2 (s). Anal. calcd for $C_{10}H_6N_3OI$: C 38.61, H 1.94, N 13.51. Found: C 38.87, H 2.01, N 13.50.

7.2. General procedure for I–Mg exchange (11→12a–d)

To at solution of **11** (1 mmol) in THF (4 mL) at −78°C, *i*PrMgCl (2.0 M in THF, 0.65 mL, 1.3 mmol) was added over 1 min. Stirring was continued for 30 min at −78°C before the electrophile (1.5 mmol) was added. After 15 min the cooling bath was removed and the mixture was warmed to rt and quenched with sat NH_4Cl (10 mL). Extraction with CH_2Cl_2 (3×25 mL), drying of the organic phase ($MgSO_4$) and removal of the solvent in vacuo gave the crude product, which was purified by FC using heptane/EtOAc as eluent.

7.2.1. 2-(4-Formylpyrazol-1-yloxy)-benzonitrile (12a). Following the general procedure with DMF as electrophile. 289 mg **11** gave 129 mg (65%) **12a** as a colourless oil, that solidified upon standing. Crystallization from heptane/EtOAc gave colourless crystals, mp 91°C, R_f (heptane/EtOAc 1:1) 0.44. ^{1}H NMR ($CDCl_3$): 6.72 (d, 1H, *J*=8.6 Hz), 7.33 (td, 1H, *J*=7.6, 1.0 Hz), 7.59 (ddd, 1H, *J*=8.6, 7.6, 1.7 Hz), 7.74 (dd, 1H, *J*=7.7, 1.7 Hz), 7.95 (d, 1H, *J*=1.0 Hz), 8.15 (d, 1H, *J*=1.0 Hz), 9.93 (s, 1H). ^{13}C NMR ($CDCl_3$): 100.9 (s), 114.0 (s), 114.2 (d), 122.1 (s), 125.6 (d), 126.4 (d), 134.0 (d), 134.8 (d), 135.9 (d), 159.5 (s), 183.3 (d). Anal. calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.80; H, 3.54, N, 19.47.

7.2.2. 2-(4-Methoxycarbonylpyrazol-1-yloxy)-benzonitrile (12b). Following the general procedure with $NCCOOCH_3$ as electrophile. 305 mg **11** gave 239 mg of a 15:1 mixture of **12b** and **8a** after FC, corresponding to an isolated yield of 94%. Crystallization from EtOAc/heptane gave analytically pure **12b** as colourless crystals, mp 116–7°C, R_f (heptane/EtOAc 3:1) 0.27. ^{1}H NMR ($CDCl_3$): 3.88 (s, 3H), 6.65 (d, 1H, *J*=8.6 Hz), 7.26–7.33 (m, 1H), 7.53–7.60 (m, 1H), 7.72 (dd, 1H, *J*=7.7, 1.7 Hz), 7.88 (d, 1H, *J*=1.0 Hz), 8.08 (d, 1H, *J*=1.0 Hz). ^{13}C NMR ($CDCl_3$): 51.7 (q), 100.8 (s), 113.7 (s), 113.9 (d), 114.1 (s), 125.4 (d), 126.4 (d), 134.0 (d), 134.7 (d), 136.4 (d), 159.9 (s), 162.2 (s). Anal. calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.29; H, 3.89, N, 17.10.

7.2.3. 2-(4-Cyanopyrazol-1-yloxy)-benzonitrile (12c). Following the general procedure with TsCN (dissolved in 1 mL THF) as electrophile. 563 mg **11** gave 328 mg (86%) **12c** as white crystals, mp 140°C (heptane/EtOAc), R_f (heptane/EtOAc 1:1) 0.61. ^{1}H NMR ($CDCl_3$): 6.74 (br d, 1H, *J*=8.6 Hz), 7.35 (td, 1H, *J*=7.6, 1.0 Hz), 7.60 (ddd, 1H, *J*=8.6, 7.6, 1.7 Hz), 7.75 (dd, 1H, *J*=7.7, 1.7 Hz), 7.78 (d, 1H, *J*=1.0 Hz), 8.08 (d, 1H, *J*=1.0 Hz). ^{13}C NMR (CDCl$_3$): 92.3 (s), 101.4 (s), 111.7 (s), 113.9 (s), 114.6 (d), 126.1 (d), 128.3 (d), 134.2 (d), 134.8 (d), 138.0 (d), 159.3 (s). Anal. calcd for $C_{11}H_6N_4O$: C, 62.86; H, 2.88; N, 26.65. Found: C, 62.67; H, 3.05, N, 26.52.

7.2.4. 2-(4-Phenylsulfanylpyrazol-1-yloxy)-benzonitrile (12d). Following the general procedure with PhSO$_2$SPh as electrophile. 291 mg **11** gave 255 mg (93%) **12d** as a colourless oil. Crystlallization from heptane/EtOAc gave colourless crystals, mp 82–83°C, R_f (heptane/EtOAc 3:1) 0.32. ^{1}H NMR (CDCl$_3$): 6.67 (dd, 1H, *J*=8.6, 0.5 Hz), 7.15–7.32 (m, 6H), 7.53 (d, 1H, *J*=1 Hz), 7.53–7.60 (m, 1H), 7.71 (dd, 1H, *J*=7.7, 1.7 Hz), 7.74 (d, 1H, *J*=1 Hz). ^{13}C NMR (CDCl$_3$): 100.6 (s), 108.8 (s), 113.8 (d), 114.2 (s), 125.1 (d), 126.1 (d), 127.2 (d), 127.6 (d), 129.1 (d), 133.9 (d), 134.7 (d), 137.0 (s), 139.5 (d), 160.2 (s). Anal. calcd for $C_{16}H_{11}SN_3O$: C, 65.51; H, 3.78; N, 14.32. Found: C, 65.37; H, 3.92, N, 14.24.

7.3. General procedure for the ring closure of 9, 12c, 12d and 14 with LDA

The substrate (1 mmol) was dissolved in THF (6 mL) under N$_2$ and cooled to −78°C before a freshly prepared solution of LDA (1.3 mmol) in THF (1 mL) was added. The cooling bath was removed, and the mixture was allowed to warm to rt over 15 min, during which dramatic colour changes took place depending on the substrate. At rt the mixture was quenched with 4N HCl (10 mL) and stirring was continued for 30 min. Water (20 mL) was added before extraction with CH$_2$Cl$_2$ (3×25 mL), drying of the organic phase (MgSO$_4$) and removal of the solvent in vacuo gave the crude products, which were purified by FC using heptane/EtOAc as eluent.

7.3.1. 3-Bromo-9-oxa-1,9a-diaza-cyclopenta[*b*]naphthalen-4-one (10). Following the general procedure. 92 mg **9** gave 89 mg (89%) **10** as off-white crystals, mp 187°C (heptane/EtOAc), R_f (heptane/EtOAc 3:1) 0.49. ^{1}H NMR (CDCl$_3$): 7.43 (ddd, 1H, *J*=8.5, 1.0, 0.5 Hz), 7.46 (ddd, 1H, *J*=7.9, 7.3, 1.0 Hz), 7.57 (s, 1H), 7.79 (ddd, 1H, *J*=8.5, 7.3, 1.7 Hz), 8.28 (ddd, 1H, *J*=9.7, 1.7, 0.5 Hz). ^{13}C NMR (CDCl$_3$): 92.2 (s), 114.4 (d), 117.9 (s), 125.3 (d), 125.9 (s), 126.8 (d), 133.4 (d), 135.8 (d), 156.6 (s), 168.8 (s). Anal. calcd for $C_{10}H_5BrN_2O_2$: C, 45.31; H, 1.90; N, 10.57. Found: C, 45.53; H, 2.16, N, 10.28.

7.3.2. 3-Cyano-9-oxa-1,9a-diaza-cyclopenta[*b*]naphthalen-4-one (13c). Following the general procedure. 99 mg **12c** gave 82 mg (82%) **13c** as colourless crystal, mp 201°C (heptane/EtOAc), R_f (heptane/EtOAc 1:1) 0.59. ^{1}H NMR (CDCl$_3$): 7.52 (d, 1H, *J*=8.5 Hz), 7.55 (ddd, 1H, *J*=8.0, 7.3, 1.0 Hz), 7.89 (ddd, 1H, *J*=8.6, 7.3, 1.7 Hz), 7.94 (s, 1H), 8.33 (ddd, 1H, *J*=8.0, 1.7, 0.4 Hz). ^{13}C NMR (CDCl$_3$): 89.8 (s), 100.9 (s), 114.7 (d), 117.7 (s), 126.2 (d), 126.9 (d), 130.7 (s), 136.7 (d), 137.2 (d), 156.8 (s), 167.3 (s). Anal. calcd for $C_{11}H_{56}N_3O_2$: C, 62.56; H, 2.39; N, 19.90. Found: C, 62.27; H, 2.42, N, 19.65.

7.3.3. 3-Phenylsulfanyl-9-oxa-1,9a-diaza-cyclopenta[*b*]-naphthalen-4-one (13d). Following the general procedure. 71 mg **12d** gave 56 mg (79%) **13d** as a slightly yellow thick oil. Crystallization from heptane/EtOAc gave colourless crystals, mp 73–74°C, R_f (heptane/EtOAc 3:1) 0.39. ^{1}H NMR (CDCl$_3$): 7.25–7.50 (m, 8H), 7.77 (ddd, 1H, *J*=8.5, 7.7, 1.7 Hz), 8.25 (dd, 1H, *J*=8.3, 1.7 Hz). ^{13}C NMR (CDCl$_3$): 113.2 (s), 114.3 (d), 118.3 (s), 125.2 (d), 126.8 (d), 127.1 (s), 127.7 (d), 129.3 (d), 131.0 (d), 133.9 (s), 134.1 (d), 135.6 (d), 156.7 (s), 169.1 (s). Anal. calcd for $C_{16}H_{10}N_2O_2S$: C, 65.29; H, 3.42; N, 9.52. Found: C, 65.03; H, 3.37, N, 9.42.

7.3.4. 3-Diphenylphosphanyl-9-oxa-1,9a-diaza-cyclopenta[*b*]naphthalen-4-one (13e). One-pot I–Mg-exchange and ring closure using (Ph)$_2$PCl as electrophile: **11** (182 mg, 0.59 mmol) was dissolved in THF (2.5 mL) and cooled to −78°C before *i*PrMgCl (2.0 M in THF, 0.38 mL, 0.76 mmol) was added over 1 min. Stirring was continued for 30 min at −78°C before (Ph)$_2$PCl (0.16 mL, 0.88 mmol) was added. The cooling bath was removed and the mixture was allowed to warm to rt over 15 min. After the mixture reached rt it was cooled to −78°C again, before a freshly prepared solution of LDA (1.18 mmol) in THF (1 mL) was added and the cooling bath was removed. At rt the mixture was worked up as described in the general procedure. FC yielded 212 mg (98%) **13e** as fluorescent yellow crystals, mp 160°C (heptane/EtOAc), R_f (heptane/EtOAc 1:1) 0.72. ^{1}H NMR (CDCl$_3$): 6.93 (d, 1H, *J*=0.9 Hz), 7.34–7.45 (m, 12H), 7.76 (ddd, 1H, *J*=8.6, 7.2, 1.7 Hz), 8.20 (ddd, 1H, *J*=7.9, 1.7, 0.4 Hz). ^{13}C NMR (CDCl$_3$): 114.3 (d), 115.3 (s(d), J_{C-P}=21 Hz), 118.2 (s), 125.1 (d), 126.8 (d), 128.6 (s(d), J_{C-P}=7 Hz), 129.1 (d), 130.0 (s(d), J_{C-P}=24 Hz), 133.4 (d(d), J_{C-P}=21 Hz), 135.5 (d), 135.7 (s(d), J_{C-P}=10 Hz), 135.9 (d(d) J_{C-P}=2 Hz), 156.8 (s), 169.3 (s). Anal. calcd for $C_{22}H_{15}PN_2O_2$: C, 71.35; H, 4.08; N, 7.56. Found: C, 71.26; H, 4.21, N, 7.54.

7.3.5. 2-(4-*p*-Tolylpyrazol-1-yloxy)-benzonitrile (14). To a solution of **11** (336 mg, 1.08 mmol) in THF (5 mL) at −78°C, *i*PrMgCl (2.0 M in THF, 0.70 mL, 1.4 mmol) was added over 1 min. Stirring was continued for 30 min at −78°C before ZnCl$_2$ (1 M in THF, 3.24 mL, 3.24 mmol) was added, and the mixture was warmed to rt. At rt, *p*-iodotoluene (471 mg, 2.16 mmol) and Pd(PPh$_3$)$_4$ (62 mg, 0.054 mmol) in DMF (3.5 mL) was added, and the mixture was stirred 18 h at rt. Quenching with sat NH$_4$Cl (20 mL) and extraction with Et$_2$O (4×25 mL), drying of the organic phases (MgSO$_4$) and removal of the solvent in vacuo gave the crude product, which was purified by FC using heptane/EtOAc as eluent giving 239 mg (80%) **14** as colourless crystals, mp 128–129°C (heptane/EtOAc), R_f (heptane/EtOAc 1:1) 0.71. ^{1}H NMR (CDCl$_3$): 2.37 (s, 3H), 6.67 (ddd, 1H, *J*=8.6, 0.9, 0.3 Hz), 7.18–7.23 (m, 2H), 7.24 (td, 1H, *J*=7.6, 1.0 Hz), 7.37–7.42 (m, 2H), 7.53 (ddd, 1H, *J*=8.6, 7.6, 1.7 Hz), 7.68 (d, 1H, *J*=1.2 Hz), 7.69 (ddd, 1H, *J*=7.6, 1.7, 0.4 Hz), 7.78 (d, 1H, *J*=1.2 Hz). ^{13}C NMR (CDCl$_3$): 20.9 (q), 100.2 (s), 113.7 (d), 114.4 (s), 119.9 (d), 122.3 (s), 124.7 (d), 125.4 (d), 128.1 (s), 129.7 (d), 131.5 (d), 133.8 (d), 134.7 (d), 137.2 (s), 160.7 (s). Anal. calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 73.89; H, 4.62, N, 14.99.

7.3.6. 3-*p*-Tolyl-9-oxa-1,9a-diaza-cyclopenta[*b*]naphthalen-4-one (15). Following the general procedure. 91 mg

14 gave 78 mg (91%) **15** as colourless crystals, mp 123°C (heptane/EtOAc), R_f (heptane/EtOAc 3:1) 0.44. ^{1}H NMR ($CDCl_3$): 2.41 (s, 3H), 7.25–7.30 (m, 2H), 7.39–7.45 (m, 2H), 7.68 (s, 1H), 7.72–7.79, m, 3H), 8.25–8.29 (m, 1H). ^{13}C NMR ($CDCl_3$): 21.1 (q), 114.1 (d), 118.4 (s), 122.7 (s), 124.9 (d), 125.3 (s), 126.9 (d), 127.2 (s), 128.8 (d), 129.2 (d), 130.6 (d), 135.4 (d), 138.2 (s), 156.3 (s), 169.9 (s). Anal. calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.88; H, 4.61, N, 10.15.

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14. A sample of **4b** dissolved in DMSO-d_6 spontaneously gave **1b** at rt without added base.
15. Crystallographic data (excluding structure factors) for the structure of **1b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 171161. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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