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FURTHER APPROACHES TO ANOMALOUS CARBON INSERTION INTO A BENZENE RING IN THE BISCHLER-NAPIERALSKI REACTION OF PHENOLIC 2-PHENYLFORMANILIDES

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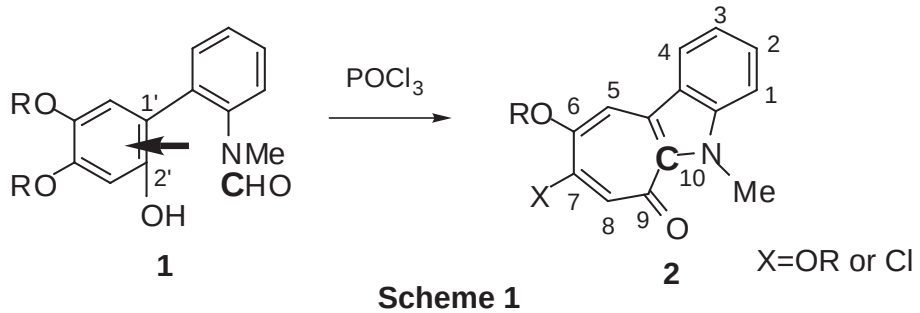
Abstract - Three phenolic 2-phenylformanilides were subjected to Bischler-Napieralski reaction for further examination of anomalous carbon insertion into a benzene ring.

Bischler-Napieralski reaction[1] (BNR) is a classical, but very important, isoquinoline construction method from amide substrates and mechanism, which is controlled by aromatic electrophilic substitution of reactive amide functions activated by a dehydrating agent such as $POCl_3$, is generally accepted. We[2] recently reported that the carbon atom of formamide functions could anomalously insert into a benzene ring in the BNR of some 2-(2,4,5-trioxygenated phenyl)-substituted aromatic *N*-methylformamides giving azaaulene products with a 7-5 ring system as structural isomers of isoquinoline skeletons, and that direction of the insertion was strictly dependent upon the oxygen functionality on the 2-benzene ring. Thus, carbon insertion into the C1-C2 bond of the 2-phenyl group was observed when 2-(4,5-dialkoxy-2-hydroxyphenyl)-*N*-methylformanilides (**1**) were used as substrates, resulting in the formation of benzo[*b*]azaazulen-9-ones (**2**) with either an alkoxy or a chloro group at the 7 position, dependent upon the reaction condition used[2b] (Scheme 1).

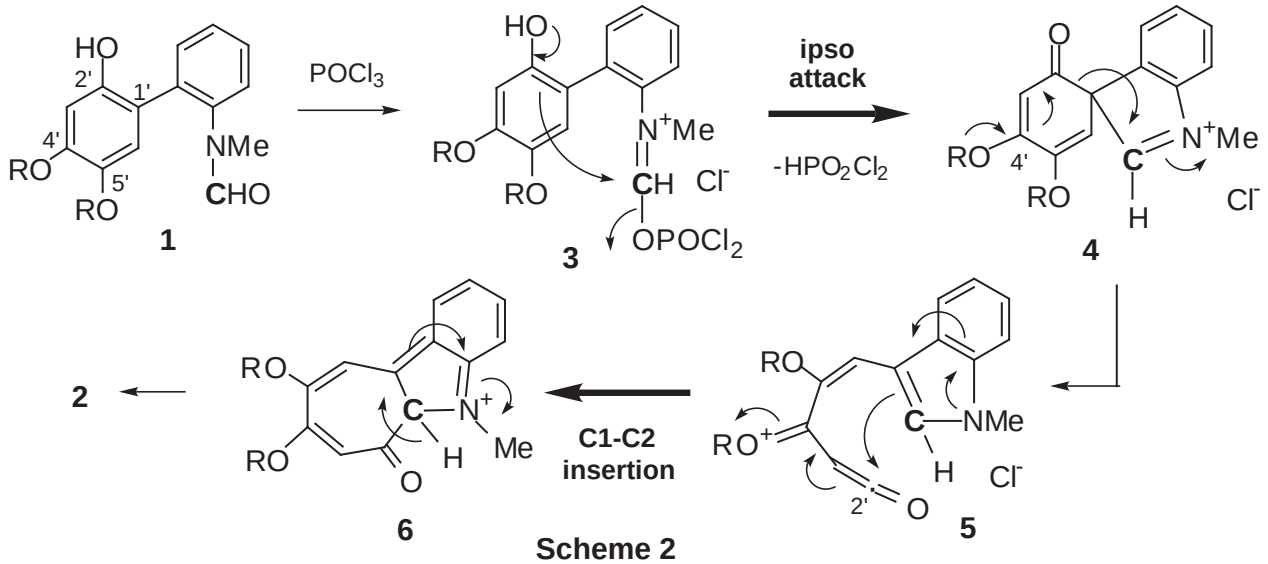


1 **2**

Scheme 1

Mechanistic consideration for the C1-C2 carbon insertion (see Scheme 2) has suggested that azaazulene products could be also formed in the cases of other functionalities on the formamide nitrogen atom and/or

lack of 5-alkoxy group in the 2-benzene ring. In this paper we present additional evidences for this anomalous carbon insertion under the conditions of BNR.



Scheme 2

We[2b] have proposed a machanism for the C1-C2 carbon insertion as shown in Scheme 2, in which an azaazulene (**2**) was given by four successive reactions of (i) formation of a spiro-indolenium-cyclohexadienone (**4**) by ipso attack of an iminium carbon to the 1 position doubly activated by 2',4'-dioxygen functions in a reactive amide (**3**), (ii) ring cleavege of the cyclohexadienone unit by participation of 4'-alkoxy group to give an indole ketene (**5**), (iii) nucleophilic attack of the enamine function on an indole skeleton to the ketene unit in **5** affording a 7-5-6 ring system (**6**), and (iv) aromatization of **6** to **2**. This mechanism suggests the possible formation of 9-azaazulenones from alternative substrates (**7**) or (**8**) carrying other functionality on the formyl group in place of an *N*-methyl group or without an 5-alkoxy substituent on the 2-benzene ring, respectively (Figure 1).

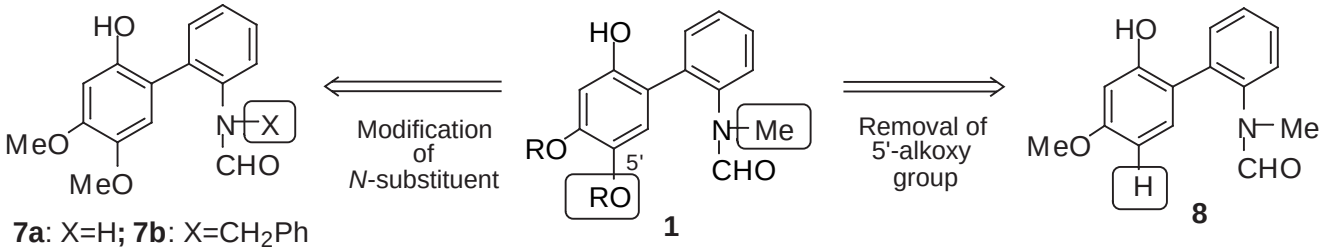
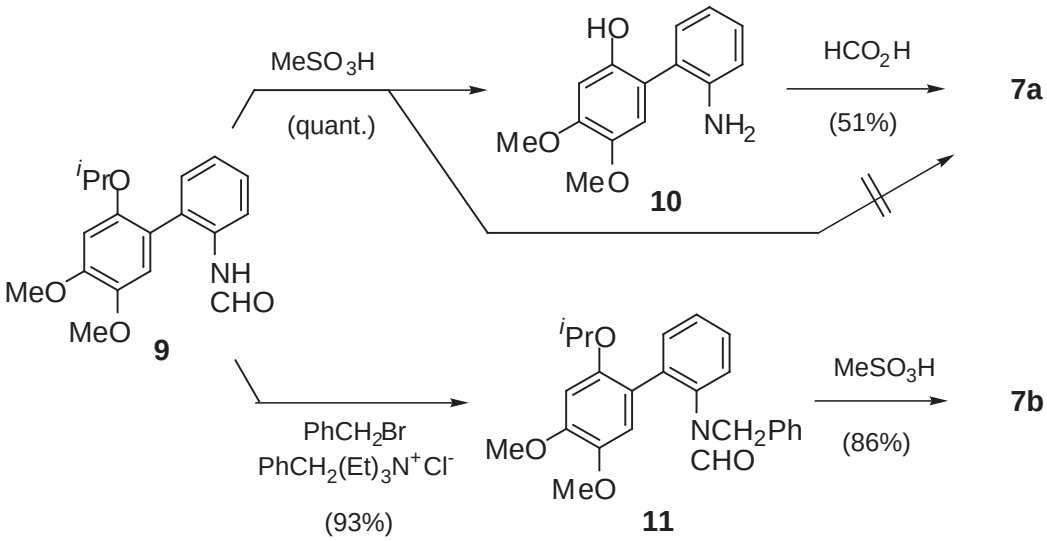


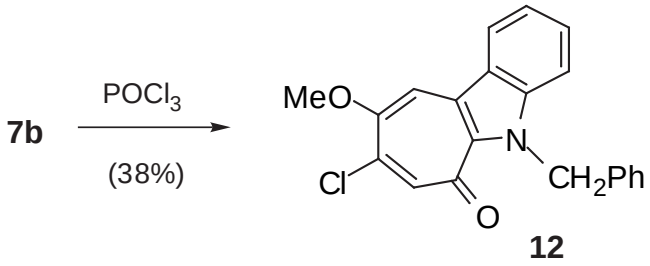
Figure 1

At first substituent effects on the nitrogen atom on the carbon insertion were examined using an *N*-unsubstituted (**7a**) and a benzyl-substituted formanilides (**7b**), which were prepared from 2-(4,5-dimethoxy-2-isopropoxyphenyl)formanilide (**9**), a synthetic precursor of the *N*-methylformanilide (**1**) (R=Me),[2b] as shown in Scheme 3. The former (**7a**) was given by successive treatment of $MeSO_3H$ and formic acid because a trial for selective deprotection of the isopropyl group in **9** with $MeSO_3H$ resulted in an additional *N*-deformylation, whereas the latter (**7b**) was smoothly prepared from **9** by modification of the reported method.[2b]



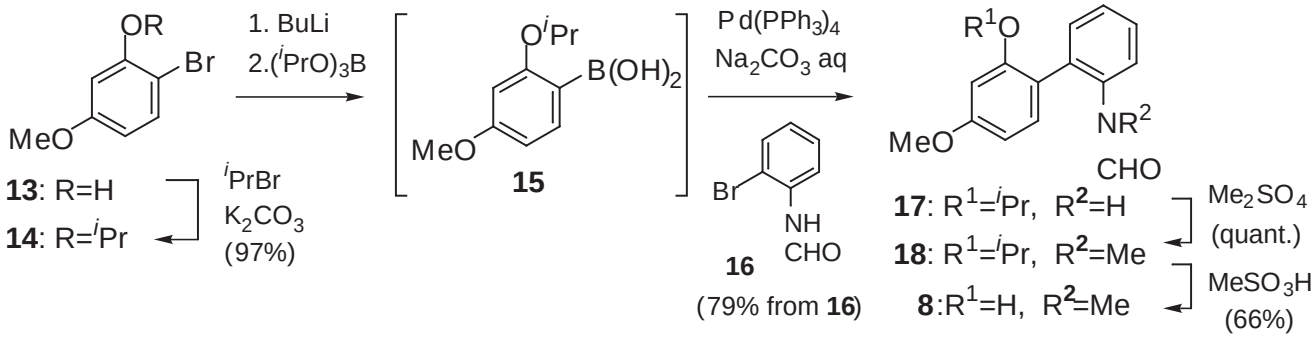
Scheme 3

The BNR of *N*-unsubstituted substrate (**7a**) with $POCl_3$ without solvent resulted in no formation of an azaazulene product. On the other hand the use of the *N*-benzyl derivative (**7b**) as a substrate under the same condition led to the production of a chloro-containing cyclized product (**12**) in 38% yield (Scheme 4). The expected construction of a 7-5 ring system was reasonably deduced by inspection of its spectral data (See **EXPERIMENTAL**).

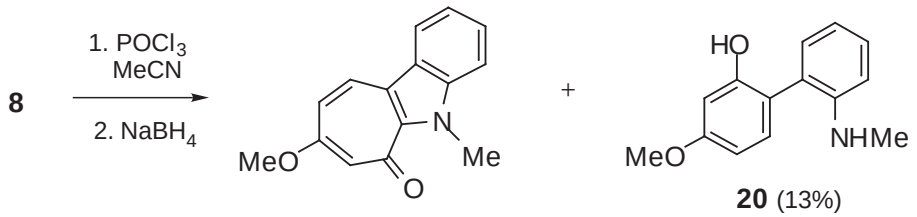


Scheme 4

We next examined the BNR of 2-(2-hydroxy-4-methoxyphenyl)-*N*-methylformanilide (**8**). The starting formanilide (**8**) was prepared from 2-bromo-5-methoxyphenol[3] (**13**) through protection of the phenol function of **13** with isopropyl group, Suzuki-type coupling reaction[4] between a boronic acid (**15**) and 2-bromoformanilide (**16**), *N*-methylation of **17**, and deprotection of **18** as shown in Scheme 5.



Scheme 5



19 (32%) + **20** (13%)

Scheme 6

Treatment of **8** with $POCl_3$ without solvent as above resulted in the formation of a complex mixture *albeit* following $NaBH_4$ reduction for easy isolation of products. However, the reaction using MeCN as solvent at 50 °C for 5 h followed by $NaBH_4$ reduction afforded a cyclized product (**19**) in 32% yield, together with a deformylated aniline derivative (**20**) (13%) (Scheme 6). Appearance of a characteristic 3H signal at lower field (δ 4.44) in the ^{1}H NMR spectrum of **19**, attributable to an *N*-methyl group, indicated the formation of a 7-5 ring system.[2b] Thus, the successful isolation of an expected azaazulene even in the case of a formanilide lacking a 5-alkoxy group strongly supports the proposed mechanism for the C1-C2 carbon insertion shown in Scheme 2.

In conclusion, it was clear that other substituents than methyl group on the formamide nitrogen may be available for the C1-C2 carbon insertion under the conditions of BNR. Furthermore, 4-alkoxy-2-hydroxy function in the 2-phenyl group of formanilides could be the minimum requirement for the C1-C2 carbon insertion.

EXPERIMENTAL

General

Mps were measured on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured with JASCO FT/IR 300E. ^{1}H NMR spectra were recorded with JEOL JNM-GSX500A (500 MHz), JNM-GSX400A (400 MHz), or JNM-ECP400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded with JNM-ECP400 (100 MHz) spectrometer. The chemical shifts are relative to TMS in $CDCl_3$. HRFABMS spectra were measured with JEOL JMS-HX110 spectrometer. Reactions were monitored by TLC on Kieselgel 60 F254 (Merck, 5715). Column chromatography was performed on silica gel (Fuji Silysia, FL100D). $POCl_3$ was used for BNR after distillation.

2-(2-Aminophenyl)-4,5-dimethoxyphenol (10). A solution of **9** (0.201 g, 0.636 mmol) and $MeSO_3H$ (1.0 mL, 15.4 mmol) in $CHCl_3$ (10 mL) was refluxed for 2 h under Ar. After dilution with $CHCl_3$ the mixture was washed with 10% aq $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a light brown oil (0.203 g, quant.), which was used for a next step without purification.

2-(4,5-Dimethoxy-2-hydroxyphenyl)formanilide (7a). A solution of **10** (0.031 g, 0.128 mmol) in 98% HCO_2H (0.7 mL, 18.9 mmol) was refluxed for 2 h. After addition of H_2O the mixture was extracted with AcOEt. The organic solution was washed with 10% aq $NaHCO_3$ and brine, dried (K_2CO_3),

and evaporated. The residue was purified by preparative TLC ($CHCl_3$: AcOEt=4 : 1) to afford colorless prisms (0.018 g, 51%), mp 187-189 ℃; IR ($CHCl_3$) ν_{max} 3556, 1678 cm^{-1}; ^1H NMR[5] (400 MHz) δ 3.83 (1/2x3H, s, OMe), 3.84 (1/2x3H, s, OMe), 3.85 (1/2x3H, s, OMe), 3.92 (1/2x3H, s, OMe), 6.51 (1/2x1H, s, ArH), 6.52 (1/2x1H, s, ArH), 6.64 (1/2x1H, s, ArH), 6.68 (1/2x1H, s, ArH), 7.24-7.46 (total 5H, m, ArH and NH), 8.13 (1/2x1H, br s, NH), 8.31 (1/3x1H, s, CHO), 8.38 (1/3x1H, d, *J*=8.3 Hz, CHO), 8.59 (1/3x1H, d, *J*=11.6 Hz, CHO); HRFABMS *m/z* 273.1010 (Calcd for $C_{15}H_{15}NO_4$: 273.1001).

***N*-Benzyl-2-(4,5-dimethoxy-2-isopropoxyphenyl)formanilide (11).** A mixture of **9** (0.151 g, 0.478 mmol), benzyltriethylammonium chloride (0.033 g, 0.146 mmol), and benzyl bromide (0.17 mL, 1.43 mmol) in benzene (1.5 mL) and 20% aq NaOH (0.75 mL) was stirred at rt for 18.5 h, poured into H_2O, and extracted with AcOEt. The organic solution was washed with brine, dried (K_2CO_3), and evaporated. Purification of the residue by column chromatography (hexane : AcOEt=2 : 1) afforded a light brown oil (0.180 g, 93%); IR (neat) ν_{max} 1669 cm^{-1}; ^1H NMR[5] (400 MHz) δ 1.13-1.23 (total 6H, m, CH(*Me*)$_2$), 3.81 (1/10x3H, s, OMe), 3.83 (9/10x3H, s, OMe), 3.92 (9/10x3H, s, OMe), 3.94 (1/10x3H, s, OMe), 4.29 (1H, septet, *J*=6.1 Hz, OC*H*(Me)$_2$), 4.44 (2H, br s, OC*H*$_2$Ph), 6.61 (1H, s, ArH), 6.63 (1H, s, ArH), 6.89-7.35 (total 9H, m, ArH), 8.30 (9/10x1H, s, CHO), 8.35 (1/10x1H, s, CHO); HRFABMS *m/z* 405.1959 (Calcd for $C_{25}H_{27}NO_4$: 405.1940).

***N*-Benzyl-2-(4,5-dimethoxy-2-hydroxyphenyl)formanilide (7b).** A solution of **11** (0.033 g, 0.082 mmol) and $MeSO_3H$ (0.13 mL, 2.00 mmol) in $CHCl_3$ (1.3 mL) was refluxed for 1 h under Ar. After addition of H_2O the mixture was extracted with $CHCl_3$. The organic solution was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by column chromatography ($CHCl_3$: AcOEt=5 : 1) afforded colorless prisms (0.026 g, 86%), mp 108.5-111 ℃ (recrystallization from MeOH); IR (Nujol) ν_{max} 1654 cm^{-1}; ^1H NMR[5] (400 MHz) δ 3.78 (1/5x3H, s, OMe), 3.80 (4/5x3H, s, OMe), 3.89 (4.5x3H, s, OMe), 3.91 (1/5x3H, OMe), 4.49 (2H, br s, OC*H*$_2$Ph), 6.55-6.62 and 6.94-7.41 (total 11H, m, ArH), 8.35 (4/5x1H, s, CHO), 8.39 (1/5x1H, s, CHO); EIMS *m/z* 363 (M^+, 6.8%); *Anal.* Calcd for $C_{22}H_{21}NO_2 \cdot 1/3MeOH$: C, 71.70; H, 6.01; N, 3.74. Found: C, 71.60; H, 5.98; N, 3.63.

BNR of Formanilide (7b) : 10-Benzyl-7-chloro-6-methoxybenz[*b*]azaazulen-9-one (12). A mixture of **7b** (0.026 g, 0.071 mmol) and $POCl_3$ (0.33 mL, 3.54 mmol) was stirred at 50 ℃ for 2 h. After evaporation of the $POCl_3$, the mixture was poured into H_2O and extracted with $CHCl_3$. The organic solution was dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC ($CHCl_3$: MeOH=20 : 1) to afford an orange oil (0.009 g, 38%), trituration of which with Et_2O afforded orange prisms, mp 148-150 ℃; IR (KBr) ν_{max} 1578 cm^{-1}; ^1H NMR (400 MHz) δ 4.10 (3H, s, OMe), 6.02 (2H, s, OC*H*$_2$Ph), 7.05 (2H, dif. d, *J*=8.2 Hz, 2'- and 6'-H), 7.22-7.53 (total 8H, m, ArH), 7.56 (1H, s, 5-H), 7.68 (1H, s, 8-H), 8.06 (1H, dif. d, *J*=8.0 Hz, 4-H); HRFABMS *m/z* 352.0938 (Calcd for $C_{21}H_{16}NO_2{}^{37}Cl$: 352.0948), 350.0934 (Calcd for $C_{21}H_{16}NO_2{}^{35}Cl$: 350.0948).

1-Bromo-2-isopropoxy-4-methoxybenzene (14). A mixture of 2-bromo-5-methoxyphenol (**13**) (4.50 g, 22.1 mmol), isopropyl bromide (6.2 mL, 66.0 mmol), and K_2CO_3 (8.00 g, 57.9 mmol) in DMF (11.4 mL) was stirred at 65 ℃ for 2.5 h under Ar. The reaction mixture was poured into H_2O and extracted with Et_2O. The ethereal solution was washed with 5% aq NaOH, H_2O, and brine, dried ($MgSO_4$), and evaporated to give a colorless oil (5.28 g, 97%), which was used for a next step without purification.

2-(2-Isopropoxy-4-methoxyphenyl)formanilide (17). A 1.68 M solution of *n*-BuLi in hexane (7.4 mL, 12.4 mmol) was slowly added to a solution of **14** (2.00 g, 8.16 mmol) in THF (20 mL) at -78℃ during 20 min and the whole was stirred at the same temperature for 1.5 h under Ar. To the mixture was added triisopropxyborane (2.8 mL, 12.1 mmol) and the whole was stirred at -78℃ for 10 min and then at rt for 4 h. The reaction mixture was poured into H_2O, acidified with 5% HCl, and extracted with AcOEt. The organic solution was washed with brine, dried ($MgSO_4$), and evaporated to give a boronic acid **15** as a brown oil (2.06 g), which was used for a next step without purification.

To a solution of 2-bromoformanilide (**16**) (1.36 g, 6.80 mmol) in benzene (7 mL) was successively added **15** prepared above, 2 M aq Na_2CO_3 (6.8 mL, 13.6 mmol), and Pd $(PPh_3)_4$ (0.235 mg, 0.204 mmol) and the whole was refluxed for 18.5 h under Ar. The reaction mixture was poured into H_2O and extracted with AcOEt. The organic solution was washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by column chromatography (hexane : AcOEt=5 : 1) afforded **17** as a light brown oil (1.54 g, 79%); IR (neat) ν_{max} 3343, 1686 cm^{-1}; ^1H NMR[5] (400 MHz) δ 1.10-1.32 (total 6H, m, CH(*Me*)$_2$), 3.85 (3H, s, OMe), 4.38 (2/5x1H, septet, *J*=6.2 Hz, OC*H*(Me)$_2$), 4.64 (3/5x1H, septet, *J*=6.2 Hz, OC*H*(Me)$_2$), 6.57-6.66 (2H, m ArH), 7.12-7.38 (total 4+3/5x1H, m, ArH), 7.71 (2/5x1H, br s, NH), 7.92 (3/5x1H, br d, *J*=10.8 Hz, NH), 8.12 (2/5x1H, d, *J*=7.9 Hz, ArH), 8.26 (2/5x1H, d, *J*=1.8 Hz, CHO), 8.52 (3/5x1H, d, *J*=11.5 Hz, CHO) ; HRFABMS *m/z* 285.1382 (Calcd for $C_{17}H_{19}NO_3$: 285.1365).

2-(2-Isopropoxy-4-methoxyphenyl)-*N*-methylformanilide (18). A mixture of **17** (1.42 g, 4.99 mmol), benzyltriethylammonium chloride (0.341 g, 1.50 mmol), and Me_2SO_4 (1.4 mL, 14.8 mmol) in benzene (14 mL) and 20% aq NaOH (7.1 mL) was stirred at rt for 3.5 h. After addition of 5% aq NH_4OH (7 mL) the whole was stirred at rt for 20 min, poured into H_2O, and extracted with AcOEt. The organic solution was washed with 5% HCl and brine, dried (K_2CO_3), and evaporated to give a brown oil (1.50 g, quant.), which was used for a next step without purification.

2-(2-Hydroxy-4-methoxyphenyl)-*N*-methylformanilide (8). A solution of **18** (0.101 g, 0.338 mmol) and $MeSO_3H$ (0.54 mL, 8.32 mmol) in $CHCl_3$ (5.4 mL) was refluxed for 1 h under Ar. After addition of H_2O the mixture was extracted with $CHCl_3$. The organic solution was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by column chromatography ($CHCl_3$: AcOEt=3 : 1) afforded colorless prisms (0.057 g, 66%), mp 167-168 ℃; IR (Nujol) ν_{max} 3227, 1655 cm^{-1}; ^1H NMR[5] (400 MHz) δ 2.92 (5/6x3H, s, NMe), 3.03 (1/6x3H, s, NMe), 3.78 (5/6x3H, s, OMe), 3.81 (1/6x3H, s, OMe), 6.49-6.58 (total 2H, m, ArH), 6.96 (1/5x1H, d, *J*=8.4 Hz, 6'-H), 7.02 (4/5x1H, d,

J=8.4 Hz, 6'-H), 7.22-7.49 (total 2H, m, ArH), 8.11 (1/6x1H, s, CHO), 8.16 (5/6x1H, s, CHO); EIMS *m/z* 257 (M^+, 63%); *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.76; H, 5.92; N, 5.31.

BNR of Formanilide (8) : 7-Methoxy-10-methylbenz[*b*]azaazulen-9-one (19) and 5-Methoxy-2-(2-methylaminophenyl)phenol (20). A solution of **8** (0.050 g, 0.195 mmol) and $POCl_3$ (0.29 mL, 3.11 mmol) in MeCN (8 mL) was stirred at 50 ℃ for 2 h. After addition of a further $POCl_3$ (0.29 mL, 3.11 mmol) the whole was stirred at 50 ℃ for 3 h and the solvent and the reagent were evaporated. The residue was dissolved in MeOH (1 mL), to which was added an excess amount of $NaBH_4$ (0.074 g, 1.96 mmol) under ice-cooling. The mixture was stirred at rt for 40 min and the solvent was evaporated. After addition of H_2O the mixture was extracted with $CHCl_3$. The organic solution was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC (hexane : AcOEt=2 : 1) to afford two products; **19**: yellow prisms (0.015 g, 32%), mp 132-135 ℃ (recrystallization from $CHCl_3$); IR ($CHCl_3$) ν_{max} 1628 cm^{-1}; ^1H NMR (400 MHz) δ 3.84 (3H, s, OMe), 4.44 (3H, s, NMe), 6.64 (1H, d, *J*=2.7 Hz, 8-H), 6.71 (1H, dd, *J*=11.7, 2.7 Hz, 6-H), 7.36 (1H, ddd, *J*=8.1, 4.8, 2.9 Hz, 3-H), 7.55 (2H, m, 1- and 2-H), 7.87 (1H, d, *J*=11.7 Hz, 5-H), 8.04 (1H, d, *J*=8.1 Hz, 4-H); ^{13}C NMR (100 MHz) δ 33.4, 55.5, 110.6, 114.4, 120.1, 120.2, 120.9, 121.7, 125.3, 127.0, 127.2, 139.4, 139.6, 165.2, 165.2, 178.7; EIMS *m/z* 239 (M^+, 4.2%); *Anal*. Calcd for $C_{15}H_{13}NO_2 \cdot 1/10CHCl_3$: C, 72.19; H, 5.25; N, 5.58. Found: C, 72.58; H, 5.44; N, 5.53. **20**: yellow prisms (0.006 g, 13%), mp 53-58 ℃; IR (Nujol) ν_{max} 3315 cm^{-1}; ^1H NMR (400 MHz) δ 2.71 (1/6x3H, s, NMe), 2.83 (5/6x3H, s, NMe), 3.83 (3H, s, OMe), 6.58-6.62 (total 2H, m, ArH), 6.85 (1H, d, *J*=7.7 Hz, 3'-H), 6.94 (1H, dd, *J*=7.7, 7.7 Hz, 5'-H), 7.18-7.21 (total 2H, m, ArH), 7.33 (1H, ddd, *J*=7.7, 7.7, 1.6 Hz, 4'-H).

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5. Complex signals were observed due to the presence of geometrical isomers on the amide bond.