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HETERODIENOPHILIC INTRAMOLECULAR DIELS-ALDER REACTIONS OF 1,2,4-TRIAZINES. SYNTHESIS OF NOVEL POLYCYCLIC CONDENSED PYRAZINES AND LUMAZINES

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Abstract - 3-(2'-Cyanophenoxy)-1,2,4-triazines and 7-(2'-cyanophenoxy)-6-azalumazines undergo intramolecular Diels-Alder reactions to yield novel polycyclic pyrazines and lumazines. However, the analogous 5-(2'-cyanophenoxy)-1,2,4-triazines fail to undergo cycloaddition, preventing access to the unknown benzfuro[2,3-e]-1,2,4-triazine system. Substitution of oxime ethers for nitriles on the dienophilic sidechains of the respective Diels-Alder precursors failed to increase their inverse electron demand Diels-Alder reactivity.

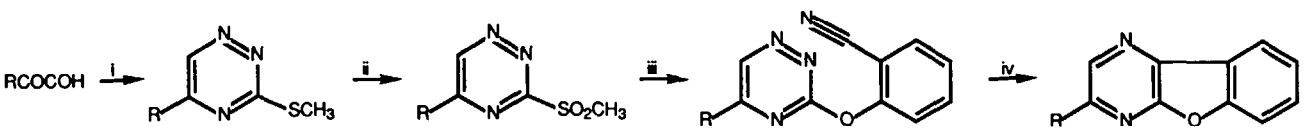
1,2,4-Triazines have received considerable attention as heterocyclic azadienes in inverse electron demand Diels-Alder reactions with electron rich dienophiles.[1] When the dienophilic component is present in a side chain tethered to the azadiene, cycloaddition proceeds with remarkable ease as a consequence of the entropic assistance inherent in intramolecular reactions. Our laboratories and others have exploited this concept by the synthesis of a wide array of bicyclic fused pyridines[2] and pyrimidines.[3] More recently, we have applied this methodology to the preparation of 6,7-annulated-5-deazapteridines[4] and are currently extending the concept to the synthesis of 5-deazafolic acid derivatives. The enhanced reactivity of intramolecular Diels-Alder reactions of 1,2,4-triazines precludes the need for electron rich dienophiles and even allows for the utilization of electron deficient dienophiles such as nitriles.[2c,5,6,7] We report herein the extension of this latter reaction to the preparation of novel tricyclic and tetracyclic condensed pyrazines, and on unsuccessful attempts to prepare the benzfuro[2,3-e]-1,2,4-triazine system.

The 3-methylthio-1,2,4-triazines **1a-e**, easily prepared by condensation of the appropriate glyoxals[8] with S-methylthiosemicarbazide,[9] were oxidized with mcpba to the methylsulfones **2a-e**.[2g] Nucleophilic displacement of methylsulfinate with sodium 2-cyanophenoxide (generated in anhydrous THF by treatment of 2-cyanophenol with sodium hydride) afforded the 3-(2'-cyanophenoxy)-1,2,4-triazines **3a-e** in good yields. Compounds **3a-e** underwent intramolecular cycloaddition in refluxing nitrobenzene (bp 210 °C) over a 9-19 h period to yield the benzfuro[2,3-b]pyrazines **4a-e** (Table 1).[10]

❖

This paper is dedicated with all good wishes to my long-time friend and colleague, Prof. Hans Wynberg, on the occasion of his sixth-fifth birthday.

Table 1. Synthesis of Benzofuro[2,3-b]pyrazines

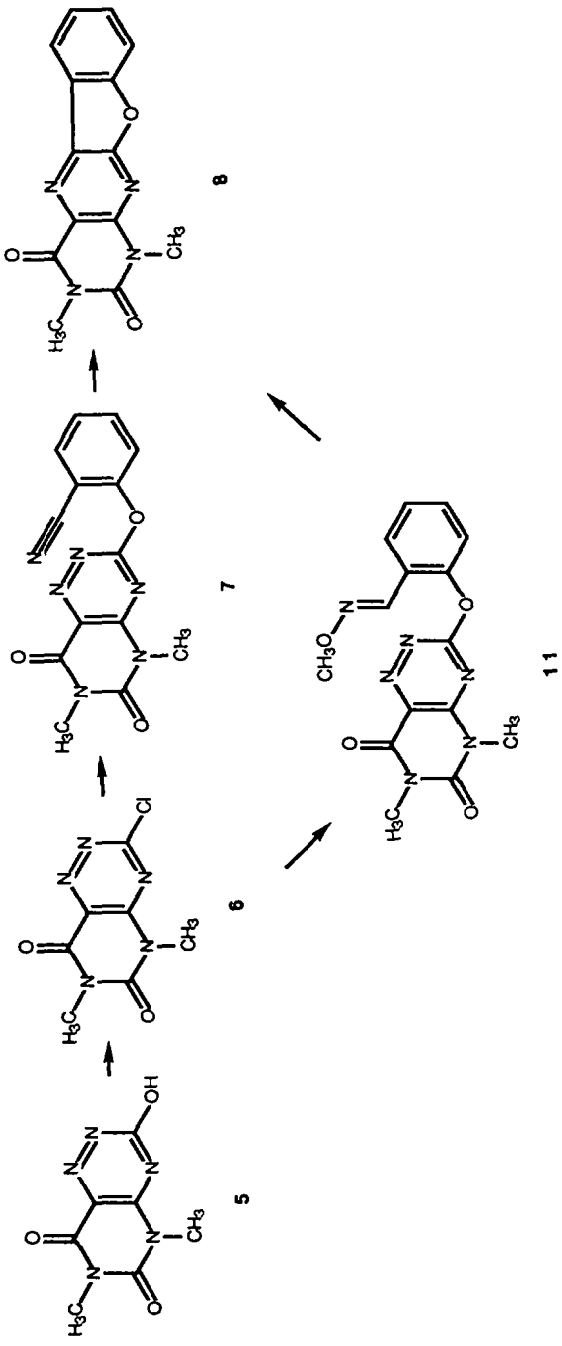


1 2 3 4

Compound	R	% Yield	
a	H	65	75
b	C_6H_5	82	81
c	4-ClC_6H_4	90	75
d	4-FC_6H_4	83	82
e	4-$CH_3OC_6H_4$	52	81

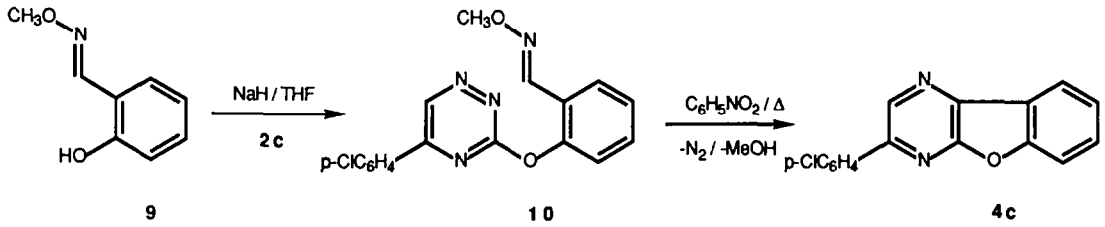
i. $H_2NNHC(SCH_3)=NH_2^+ I^-$ / $NaHCO_3$ ii. mcpba iii. sodium 2-cyanophenoxide iv. $C_6H_5NO_2$ / Δ / 9-19 h.

Scheme 1



It seemed reasonable to expect that substitution of an electron rich nitrile equivalent such as an oxime ether for the electron deficient nitrile in this inverse electron demand Diels-Alder reaction might increase the facility of the cycloaddition reaction by decreasing the HOMOdienophile/LUMOdiene energy gap, thus providing more favorable frontier orbital overlap.[12,13] Accordingly, salicylaldehyde O-methyloxime **9**[14] was deprotonated with sodium hydride in anhydrous THF and subsequently treated with the 3-methylsulfonyl-1,2,4-triazine **2c** to yield **10**. However, when a solution of **10** was refluxed in nitrobenzene, it was only slowly consumed over the course of 3 days (reaction followed by tlc) to afford a meager 8% of the benzofuro[2,3-b]pyrazine **4c** (Scheme 2). The 7-chloro-6-azalumazine **6** was likewise treated with the anion of **9** to afford **11** in excellent yield. However, when **11** was subjected to analogous thermal conditions as described for **10**, only a trace amount of the desired condensed lumazine **8** could be isolated (as determined by ^{1}H NMR and HRMS) (Scheme 1). These surprising failures may be related both to the added bulk contributed by the methoxy substituent, and to conformational difficulties related to the higher electron density of the oxime ether relative to the nitrile dienophilic sidechain.

Scheme II



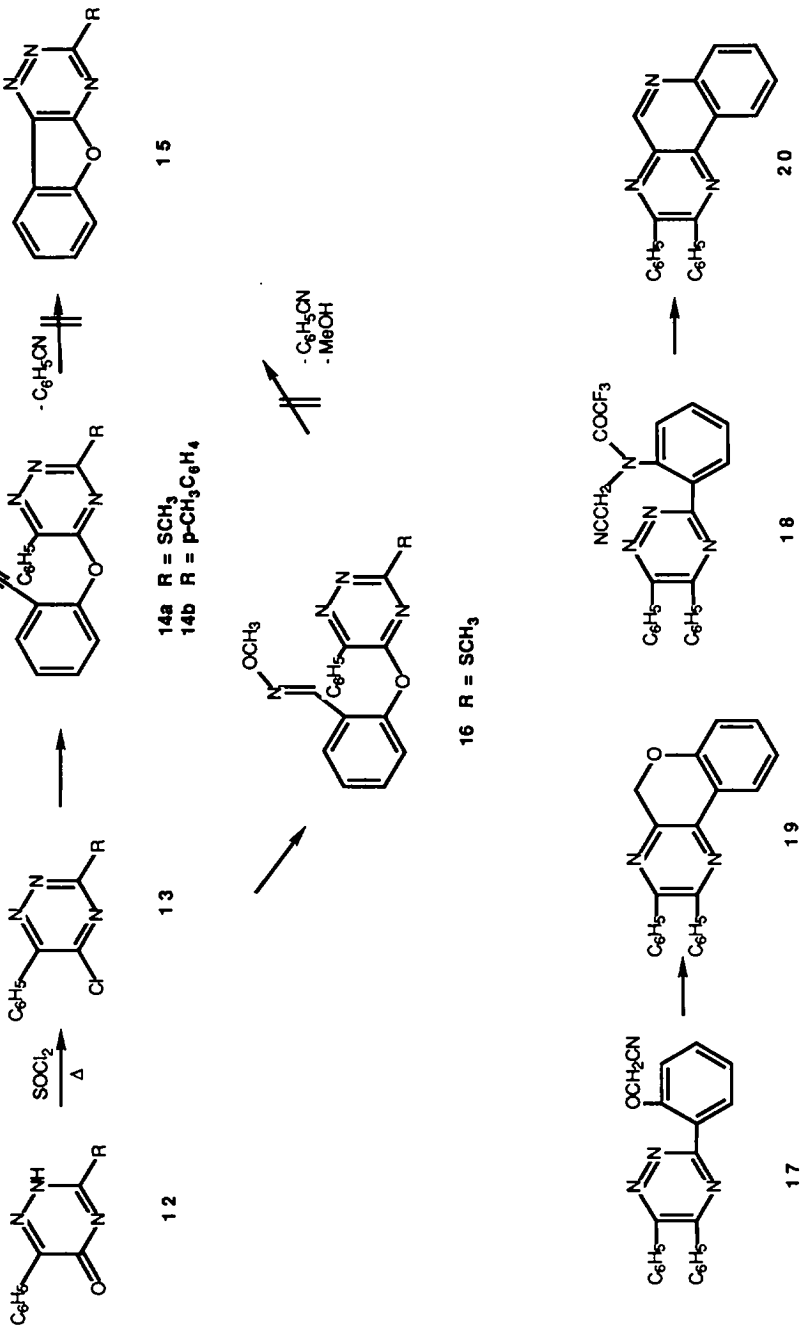
9 **10** **4c**

Our laboratories have demonstrated that when a dienophilic side chain is tethered to C5 of the 1,2,4-triazine ring, subsequent intramolecular cycloaddition yields condensed bicyclic pyrimidines via selective extrusion of a nitrile from the initial cycloadduct.[3] Extrapolation of this concept to systems carrying nitrile dienophiles posed the possibility of synthesizing the novel benzfuro[2,3-e]-1,2,4-triazine system (**15**). Thus, the 1,2,4-triazin-5-ones **12a-b** were converted with thionyl chloride to the 5-chloro-1,2,4-triazines **13a-b**,[3] which were then treated with sodium 2-cyanophenoxide as described previously for **2a-c** to give the 5-(2'-cyanophenoxy)-1,2,4-triazines **14a-b** in good yields. However, refluxing a solution of **14a** in nitrobenzene for several days resulted in no discernable reaction. In the higher boiling solvent diphenyl ether (bp 259 °C), **14a-b** was degraded over the course of 2-4 days to unidentifiable products. No trace of the desired benzfuro[2,3-e]-1,2,4-triazines **15a-b** was observed (Scheme 3).

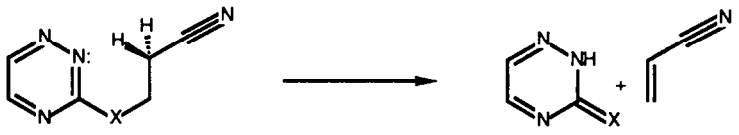
Substitution of an oxime ether for the nitrile dienophile failed to facilitate the inverse electron demand Diels-Alder reaction leading to **15**, as anticipated from the above results with **11**. Treatment of the phenoxy anion of salicylaldehyde O-methyloxime **9** with **13a** afforded the nucleophilic displacement product **16** in reasonable yield, but heating **16** in refluxing nitrobenzene over a period of 5 days merely led to extensive degradation; none of the desired benzfuro[2,3-e]-1,2,4-triazine **15a** was obtained (Scheme 3).

The utilization of nitrile dienophiles in intramolecular Diels-Alder reactions of 1,2,4-triazines becomes impractical when the nitrile is part of an aliphatic side chain tethered through a heteroatom (N, O, S) to the 1,2,4-triazine ring. In such systems, the side chain is prone to undergo a competitive thermal cleavage in a manner that can be classified either as an ene reaction or a retrograde Michael reaction (Scheme 4).[15,16] Thus, to effectively exploit the synthetic potential of nitrile dienophiles in intramolecular Diels-Alder reactions of 1,2,4-triazines, this competitive process must be blocked. As described above, the 3-(2'-cyanophenoxy)-1,2,4-triazines **3a-e** and the analogous 7-(2'-cyanophenoxy)-6-azalumazine **7** are illustrative of such systems, as are 5,6-diphenyl-3-(2'-cyanomethoxy)phenyl-1,2,4-triazine (**17**)

Scheme III


SOCl2
Δ
- C6H5CN
- C6H5CN
- MeOH
14a R = SCH3
14b R = p-CH3C6H4
16 R = SCH3
12
13
15
16
17
18
19
20

Scheme IV



and 5,6-diphenyl-3-(2'-cyanomethyltrifluoroacetamido)phenyl-1,2,4-triazine (**18**), which we have shown previously to cyclize thermally to the condensed pyrazines **19** and **20** respectively.[2c] With judicious construction of the dienophilic side chain, therefore, nitrile dienophiles can be used advantageously for the construction of novel condensed heterocyclic systems.

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1320 instrument and are reported in cm^{-1}. ^1H NMR data were obtained with a General Electric QE300 300 MHz instrument and chemical shifts are reported in ppm downfield from TMS. Mass spectral data were obtained by Dr. Dorothy Little on a Kratos MS50TC spectrometer. Elemental analyses were performed by Eli Lilly and Co., Indianapolis, Indiana. Column chromatography was performed on Merck silica gel 60 (240-400 mesh). Preparative TLC was carried out on Analtech silica gel GF uniplates (1500 microns).

Commercial reagents were utilized without further purification. Anhydrous solvents were distilled before use - tetrahydrofuran from benzophenone ketyl and methylene chloride and dimethylformamide from calcium hydride.

5-(4'-Methoxyphenyl)-3-methylsulfonyl-1,2,4-triazine (**2e**). Prepared according to the method of Taylor, Macor and Pont.[2g] Isolated as a pale yellow solid (96 %), mp 149-150 °C. IR (KBr) 3010, 2930, 2840, 1600, 1540, 1510, 1475, 1415, 1330, 1295, 1220, 1205, 1180, 1135, 1080, 1025, 985, 840, 785, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 8.30 (d, J = 8.9 Hz, 2 H), 7.10 (d, J = 9.0 Hz, 2 H), 3.94 (s, 3 H), 3.53 (s, 3 H).

HRMS Calcd for $C_{11}H_{11}N_3O_3S$: m/z 265.0521; found: 265.0520.

Synthesis of 3-(2'-Cyanophenoxy)-1,2,4-triazines (**3a-e**). General Procedure. To a stirred suspension of sodium hydride (1.02 eq, 80% oil dispersion) in anhydrous THF was added a solution of 2-cyanophenol (1.00 eq) in anhydrous THF. When the initial effervescence subsided, a THF solution of the appropriate 3-methylsulfonyl-1,2,4-triazine (**2a-e**) (1.00 eq) was added rapidly to the mixture which was subsequently stirred under nitrogen for 15.5 h. After this period, the reaction mixture was evaporated under reduced pressure, and the residual paste was taken up in methylene chloride and washed successively with 2 portions of water and one portion of brine, then dried (anhyd $MgSO_4$) and evaporated under reduced pressure to afford the crude solid product. Trituration in 1:1 ether/petroleum ether yielded the 3-(2'-cyanophenoxy)-1,2,4-triazine (**3a-e**) which was further purified as necessary as indicated below.

3-(2'-Cyanophenoxy)-1,2,4-triazine (**3a**). Obtained as a pale yellow solid (65 %), mp 77.5-78.5 °C. IR (KBr) 3100, 3060, 2250, 1615, 1560, 1545, 1500, 1460, 1415, 1375, 1295, 1240, 1195, 1175, 1120, 1065, 920, 895, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.17 (d, J = 2.1 Hz, 1 H), 8.57 (d, J = 2.3 Hz, 1 H), 7.80-7.71 (m, 2 H), 7.47-7.40 (m, 2 H).

Anal. Calcd for $C_{10}H_6N_4O$: C, 60.61; H, 3.05; N, 28.27; Found: C, 60.42; H, 3.29; N, 27.97.

3-(2'-Cyanophenoxy)-5-phenyl-1,2,4-triazine (**3b**). Obtained as a pale yellow solid (82 %), mp 144-145 °C. IR (KBr) 3070, 3030, 2230, 1595, 1540, 1505, 1480, 1435, 1420, 1345, 1305, 1270, 1220, 1180, 1065, 1000, 930, 765, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.58 (s, 1 H), 8.19-8.16 (m, 2 H), 7.81-7.71 (m, 2 H), 7.66-7.55 (m, 3 H), 7.47-7.42 (m, 2 H).

Anal. Calcd for $C_{16}H_{10}N_4O$: C, 70.07; H, 3.67; N, 20.43; Found: C, 69.76; H, 3.38; N, 20.28.

5-(4'-Chlorophenyl)-3-(2'-cyanophenoxy)-1,2,4-triazine (**3c**). Obtained as an off-white solid (90 %), mp 143.5-144.5 °C. IR (KBr) 3060, 2220, 1585, 1540, 1500, 1475, 1440, 1410, 1390, 1340, 1310, 1290, 1270, 1220, 1170, 1080, 1065, 1000, 920, 825, 770, 745 cm^{-1}; ^1H NMR

($CDCl_3$) δ 9.55 (s, 1 H), 8.15-8.11 (m, 2 H), 7.81-7.71 (m, 2 H), 7.57 (d, J = 8.6 Hz, 2 H), 7.47-7.42 (m, 2 H).

Anal. Calcd for $C_{16}H_9ClN_4O$: C, 62.25; H, 2.94; N, 18.15; Cl, 11.48; Found: C, 62.13; H, 3.05; N, 18.12; Cl, 11.73.

HRMS Calcd for $C_{16}H_9ClN_4O$: m/z 308.0465; found: 308.0469.

3-(2'-Cyanophenoxy)-5-(4'-fluorophenyl)-1,2,4-triazine **(3d)**. Obtained as a white solid (83 %), mp 123.5-124.5 °C. IR (KBr) 2230, 1600, 1540, 1505, 1480, 1420, 1400, 1355, 1315, 1285, 1275, 1230, 1195, 1160, 1065, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.54 (s, 1 H), 8.23-8.18 (m, 2 H), 7.81-7.71 (m, 2 H), 7.46-7.41 (m, 2 H), 7.29-7.24 (m, 2 H).

Anal. Calcd for $C_{16}H_9FN_4O$: C, 65.75; H, 3.10; N, 19.17; F, 6.50; Found: C, 65.69; H, 3.23; N, 19.32; F, 6.69.

HRMS Calcd for $C_{16}H_9FN_4O$: m/z 292.0760; found: 292.0761.

3-(2'-Cyanophenoxy)-5-(4'-methoxyphenyl)-1,2,4-triazine **(3e)**. Obtained as white needles (52 %), mp 161-161.5 °C, after purification by column chromatography (1:1 hexanes/ethyl acetate). IR (KBr) 3060, 2920, 2230, 1605, 1545, 1515, 1480, 1445, 1355, 1335, 1310, 1290, 1265, 1230, 1170, 1100, 1020, 1000, 935, 830, 765, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.48 (s, 1 H), 8.16 (d, J = 8.9 Hz, 2 H), 7.79-7.69 (m, 2 H), 7.45-7.39 (m, 2 H), 7.06 (d, J = 9.0 Hz, 2 H), 3.92 (s, 3 H).

Anal. Calcd for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41; Found: C, 66.85; H, 4.16; N, 18.65.

Intramolecular Diels-Alder Reactions of 3-(2'-Cyanophenoxy)-1,2,4-triazines (3a-e). Synthesis of Benzfuro[2,3-b]pyrazines **(4a-e)**. General Procedure. A stirred solution of the 3-(2'-cyanophenoxy)-1,2,4-triazine **(3a-e)** in nitrobenzene (approx 0.40 g in 10 mL solvent) was heated at reflux under nitrogen for 14-20.5 h. After this period, the reaction mixture was cooled to rt and filtered through a silica gel pad eluting successively with methylene chloride and 1:1 hexanes/ethyl acetate. The second fraction was evaporated under reduced pressure to afford the crude benzfuro[2,3-b]pyrazine **(4a-e)** which was purified as necessary as described below.

Benzfuro[2,3-b]pyrazine **(4a)**. Obtained as white needles (75 %), mp 89-90 °C, after purification by column chromatography (1:1 hexanes/ethyl acetate eluent). IR (KBr) 3180, 3150, 1620, 1465, 1445, 1370, 1355, 1270, 1165, 1100, 840, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.64 (d, J = 2.8 Hz, 1 H), 8.40 (d, J = 2.7 Hz, 1 H), 8.24 (d, J = 7.4 Hz, 1 H), 7.71-7.64 (m, 2 H), 7.53-7.48 (m, 1 H).

HRMS Calcd for $C_{10}H_6N_2O$: m/z 170.0480; found: 170.0476.

2-Phenylbenzfuro[2,3-b]pyrazine **(4b)**. Obtained as white needles (81 %), mp 149-150 °C, after purification by column chromatography (methylene chloride eluent) and subsequent trituration with petroleum ether. IR (KBr) 3100, 3060, 1620, 1480, 1450, 1430, 1370, 1335, 1305, 1280, 1180, 1105, 1085, 925, 900, 845, 770, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.13 (s, 1 H), 8.26 (d, J = 7.5 Hz, 1 H), 8.19-8.16 (m, 2 H), 7.73-7.49 (m, 6 H).

Anal. Calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38; Found: C, 77.80; H, 4.16; N, 11.17.

2-(4'-Chlorophenyl)benzfuro[2,3-b]pyrazine **(4c)**. Method A. Obtained as described above as pale white crystals (75 %), mp 182-183 °C, after purification by column chromatography (methylene chloride eluent) and subsequent trituration with petroleum ether. IR (KBr) 3050, 1475, 1440, 1400, 1370, 1170, 1090, 1000, 910, 825, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.09 (s, 1 H), 8.25 (d, J = 7.8 Hz, 1 H), 8.14-8.10 (m, 2 H), 7.73-7.65 (m, 2 H), 7.55-7.49 (m, 3 H).

Anal. Calcd for $C_{16}H_9ClN_2O$: C, 68.46; H, 3.23; N, 9.98; Cl, 12.63; Found: C, 68.10; H, 2.95; N, 9.67; Cl, 12.67.

Method B: A stirred solution of **6** (0.31 g, 0.91 mmol) in nitrobenzene (9 mL) was heated to reflux under a $CaCl_2$ drying tube for 74 h. After this time, the reaction mixture was filtered through a silica gel pad eluting successively with 100 mL each of 3:2 methylene chloride / hexanes and methylene chloride. The second fraction was evaporated under reduced pressure, and the residual material was purified by preparative tlc (methylene chloride eluent) to yield **4c** as a pale orange solid (0.02 g, 8%). The spectral and physical properties of this material were consistent with the spectral and physical properties described above for **4c**.

2-(4'-Fluorophenyl)benzfuro[2,3-b]pyrazine **(4d)**. Obtained as white plates (82 %), mp 166.5-167 °C, after purification by column chromatography (methylene chloride eluent). IR (KBr) 3050, 1590, 1500, 1475, 1400, 1365, 1305, 1270, 1225, 1170, 1095, 830, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.07 (s, 1 H), 8.24 (d, J = 7.7 Hz, 1 H), 8.19-8.14 (m, 2 H), 7.72-7.63 (m, 2 H), 7.54-7.49 (m, 1 H), 7.29-7.22 (m, 2 H).

Anal. Calcd for $C_{16}H_9FN_2O$: C, 72.72; 3.43; N, 10.60; F, 7.19; Found: C, 72.79; H, 3.30; N, 10.74; F, 7.28.

2-(4'-Methoxyphenyl)benzfuro[2,3-b]pyrazine **(4c)**. Obtained as a tan solid (81 %), mp 157-157.5 °C, after purification by column chromatography (1:1:1 hexanes/methylene chloride/ethyl acetate eluent). IR (KBr) 1600, 1540, 1510, 1480, 1445, 1370, 1320, 1275, 1250, 1170, 1025, 915, 820, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 8.21 (d, J = 7.6 Hz, 1 H), 8.13 (d, J = 8.8 Hz, 2 H), 7.70-7.60 (m, 2 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.07 (d, J = 8.9 Hz, 2 H), 3.90 (s, 1 H).

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14; Found: C, 73.63; H, 4.24; N, 10.13.

7-(2'-Cyanophenoxy)-1,3-dimethyl-6-azalumazine **(7)**. A stirred suspension of sodium hydride (0.11 g, 3.67 mmol, 80 % oil dispersion) in anhydrous THF (15 mL) was treated with a suspension of 2-cyanophenol (0.40 g, 3.36 mmol) in anhydrous THF (10 mL). After the initial effervescence subsided, a suspension of 7-chloro-1,3-dimethyl-6-azalumazine **6**[11] (0.74 g, 3.25 mmol) in anhydrous methylene chloride (100 mL) was added rapidly to the mixture which was subsequently stirred under nitrogen for 18 h. After this period, the reaction mixture was washed with water (2 x 75 mL), dried (anhyd $MgSO_4$) and evaporated under reduced pressure to afford a flaky pink solid. This material was triturated with ether to yield 7-(2'-cyanophenoxy)-1,3-dimethyl-6-azalumazine **7** as a pale pink powder (0.96 g, 95 %), mp 215.5-217 °C. IR (KBr) 2950, 2210, 1730, 1680, 1535, 1470, 1450, 1380, 1335, 1300, 1270, 1130, 1085, 1045, 1015, 810, 765, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81-7.73 (m, 2 H), 7.51-7.43 (m, 2 H), 3.58 (s, 3 H), 3.55 (s, 3 H).

Anal. Calcd for $C_{14}H_{10}N_6O_3$: C, 54.20; H, 3.25; N, 27.09; Found: C, 53.95; H, 3.16; N, 26.82.

HRMS Calcd for $C_{14}H_{10}N_6O_3$: m/z 310.0814; found: 310.0804.

1,3-Dimethyl-1,2,3,4-tetrahydrobenzfuro[3',2':5,6]pyrazino[2,3-d]pyrimidin-2,4-dione **(8)**. Method A. A stirred suspension of **7** (0.71 g, 2.29 mmol) in nitrobenzene (10 mL) was heated at reflux under nitrogen for 2 weeks. After this period, the reaction mixture was filtered through a silica gel pad, eluting successively with methylene chloride (200 mL) and 1:1 methylene chloride / ethyl acetate (400 mL). The second fraction was evaporated under reduced pressure to a volume of 20 mL, cooled with an ice bath, then vacuum filtered to afford **8** as a pale tan solid (0.15 g, 23 %), mp 295-303 °C. IR (KBr) 3110, 2940, 1720, 1660, 1590, 1555, 1510, 1410, 1350, 1320, 1255, 1170, 1120, 1035, 850, 810, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (d, J = 8.1 Hz, 1 H), 7.69-7.68 (m, 2 H), 7.57-7.51 (m, 1 H), 3.81 (s, 3 H), 3.61 (s, 3 H).

HRMS Calcd for $C_{14}H_{10}N_4O_3$: m/z 282.0753; found: 282.0725.

Method B: A stirred suspension of **11** (0.70 g, 2.05 mmol) in nitrobenzene (10 mL) was heated at reflux under nitrogen for 78.5 h. After this period, the reaction mixture was filtered through a silica gel pad, eluting successively with methylene chloride (200 mL) and 1:1 methylene chloride / ethyl acetate (200 mL). The second fraction was evaporated under reduced pressure, and the residual crimson oil was purified by preparative tlc (1:1 hexanes/ethyl acetate eluent) to yield **8** in trace yield as verified by ^1H NMR ($CDCl_3$) and HRMS. These spectral data corresponded satisfactorily with the spectral data described above for **8** prepared by Method A.

5-(4'-Chlorophenyl)-3-[2'-(methoxyimino)phenoxy]-1,2,4-triazine **(10)**. A stirred suspension of sodium hydride (0.23 g, 7.67 mmol, 80 % oil dispersion) in anhydrous THF (25 mL) was treated with salicylaldehyde O-methyloxime (**9**) (1.10 g, 7.27 mmol) at once. When the initial effervescence subsided, a suspension of 5-(4'-chlorophenyl)-3-methylsulfonyl-1,2,4-triazine (**2c**) (1.96 g, 7.27 mmol) in anhydrous THF (50 mL) was added to the reaction mixture at once. The resultant mixture was stirred under nitrogen for 20 h. After this period, the reaction mixture was evaporated under reduced pressure, and the residual yellow paste was taken up in methylene chloride (75 mL) and washed successively with water (2 x 75 mL) and brine (50 mL), dried (anhyd $MgSO_4$) and evaporated under reduced pressure to afford a yellow solid. Trituration of this material in ether yielded **10** (1.80 g, 73 %) as yellow flakes, mp 91-93 °C. IR (KBr) 2930, 1590, 1540, 1500, 1420, 1360, 1300, 1275, 1225, 1090, 1055, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.49 (s, 1 H), 8.22 (s, 1 H), 8.07 (d, J = 8.6 Hz, 2 H), 7.91-7.88 (m, 1 H), 7.53 (d, J = 8.6 Hz, 2 H), 7.51-7.46 (m, 1 H), 7.37-7.32 (m, 1 H), 7.29-7.26 (m, 1 H), 3.85 (s, 3 H).

Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44; Cl, 10.40; Found: C, 60.13; H, 4.00; N, 16.29; Cl, 10.55.

HRMS Calcd for $C_{17}H_{13}ClN_4O_2$: m/z 340.0727; found: 340.0715.

1,3-Dimethyl-7-[2'-(methoxyimino)phenoxy]-6-azalumazine **(11)**. A stirred suspension of sodium hydride (0.12 g, 4.0 mmol, 80 % oil dispersion) in anhydrous THF (15 mL) was treated with a solution of **9** (0.55 g, 3.64 mmol) in anhydrous THF (5 mL) at once. After the initial effervescence subsided, a suspension of **6** (0.82 g, 3.60 mmol) in anhydrous methylene chloride (110 mL) was added rapidly to the reaction mixture which was subsequently stirred under

nitrogen for 8 h. After this period, the reaction mixture was successively washed with water (2 x 60 mL) and brine (60 mL), and then dried (anhyd $MgSO_4$) and evaporated under reduced presssure to afford a pinkish-white solid. This material was triturated in ether to yield **11** as fine white crystals (1.15 g, 93 %), mp 245-249 °C (effervescent dec). IR (KBr) 3000, 2970, 2950, 2930, 2820, 1730, 1680, 1600, 1540, 1500, 1475, 1445, 1405, 1390, 1360, 1305, 1285, 1240, 1220, 1180, 1140, 1105, 1040, 920, 810, 760, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (s, 1 H), 7.86-7.82 (m, 1 H), 7.52-7.46 (m, 1 H), 7.40-7.35 (m, 1 H), 7.25 (d, J = 8.1 Hz, 1 H), 3.83 (s, 3 H), 3.55 (s, 3 H), 3.47 (s, 3 H).

HRMS Calcd for $C_{15}H_{14}N_6O_4$: m/z 342.1076; found: 342.1076.

5-(2'-Cyanophenoxy)-3-methylthio-6-phenyl-1,2,4-triazine **(14a).** A stirred suspension of sodium hydride (0.27 g, 9.0 mmol, 80 % oil dispersion) in anhydrous THF (15 mL) was treated with a solution of 2-cyanophenol (1.06 g, 8.86 mmol) in anhydrous THF (10 mL). When the initial effervescence subsided, a solution of freshly prepared 5-chloro-3-methylthio-6-phenyl-1,2,4-triazine (**13a**) (8.77 mmol) in anhydrous THF (15 mL) was added to the reaction mixture which was then stirred under nitrogen for 20 h. After this period, the reaction mixture was evaporated under reduced pressure, and the residual dirty white paste was taken up in methylene chloride (75 mL) and washed with water (2 x 75 mL). The organic layer was dried (anhyd $MgSO_4$) and evaporated under reduced pressure to afford a pale yellow solid. Trituration of this material in 1:1 ether/petroleum ether yielded 5-(2'-cyanophenoxy)-3-methylthio-6-phenyl-1,2,4-triazine (**14a**) as a fluffy white solid (2.17 g, 77%), mp 137-138 °C. IR (KBr) 2230, 1600, 1530, 1470, 1430, 1360, 1335, 1305, 1220, 1190, 1170, 1100, 970, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22-8.19 (m, 2 H), 7.81-7.78 (m, 1 H), 7.75-7.69 (m, 1 H), 7.61-7.55 (m, 3 H), 7.46 (t, J = 7.8 Hz, 1 H), 7.34 (d, J = 8.5 Hz, 1 H), 2.55 (s, 3 H).

Anal. Calcd for $C_{17}H_{12}N_4OS$: C, 63.74; H, 3.78; N, 17.49; S, 10.01; Found: C, 63.86; H, 3.88; N, 17.40; S, 10.24.

HRMS Calcd for $C_{17}H_{12}N_4OS$: m/z 320.0732; found: 320.0734.

5-(2'-Cyanophenoxy)-6-phenyl-3-p-tolyl-1,2,4-triazine **(14b).** Prepared as described above for **14a** from sodium hydride (0.31 g, 10.3 mmol, 80% oil dispersion), 2-cyanophenol (1.19 g, 10.0 mmol) and **13b** (1.00 mmol), and obtained as a pale yellow solid (3.28 g, 90%), mp 188.5-189.5 °C. IR (KBr) 2230, 1600, 1470, 1435, 1400, 1370, 1250, 1225, 1170, 1125, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35-8.32 (m, 2 H), 8.18 (d, J = 8.2 Hz, 2 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.80-7.74 (m, 1 H), 7.63-7.58 (m, 3 H), 7.53-7.48 (m, 1 H), 7.43 (d, J = 8.1 Hz, 1 H), 7.27 (d, J = 8.3 Hz, 2 H), 2.42 (s, 3 H).

Anal. Calcd for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.37; Found: C, 75.54; H, 4.36; N, 15.58.

HRMS Calcd for $C_{23}H_{16}N_4O$: m/z 364.1324; found: 364.1328.

5-[2'-(Methoxyimino)phenoxyl-3-methylthio-6-phenyl-1,2,4-triazine **(16).** Prepared as above for **14a** from sodium hydride (0.23 g, 7.7 mmol, 80% oil dispersion), **9** (1.08 g, 7.12 mmol), and **13a** (7.12 mmol), and obtained as a white flaky solid (1.92 g, 77 %), mp 145-146 °C. IR (KBr) 3000, 2960, 2930, 2890, 2820, 1605, 1535, 1500, 1480, 1450, 1435, 1375, 1340, 1310, 1290, 1245, 1225, 1195, 1170, 1095, 1050, 990, 980, 920, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26-8.23 (m, 2 H), 8.00 (s, 1 H), 7.76-7.72 (m, 1 H), 7.56-7.53 (m, 3 H), 7.50-7.44 (m, 1 H), 7.39-7.34 (m, 1 H), 7.18-7.15 (m, 1 H), 3.76 (s, 3 H), 2.44 (s, 3 H).

Anal. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90; S, 9.10. Found: C, 61.10; H, 4.59; N, 15.67; S, 9.12. HRMS Calcd for $C_{18}H_{16}N_4O_2S$: m/z 352.0994; found: 352.0993.

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